Probuphine
(BUPRENORPHINE HYDROCHLORIDE IMPLANT)

Psychopharmacologic Drugs Advisory Committee

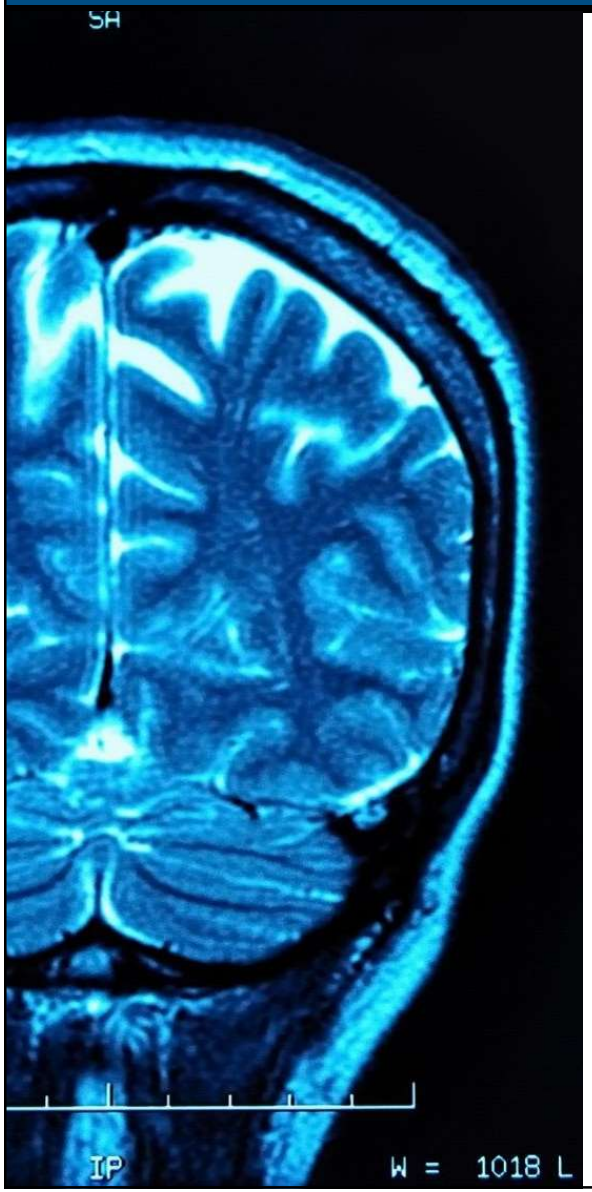
January 12, 2016

Braeburn
pharmaceuticals

Introduction

Behshad Sheldon
President and CEO
Braeburn Pharmaceuticals

Braeburn Mission



- **Focus on long-acting medicines in neuroscience**
  - Opioid addiction (buprenorphine)
  - Pain (buprenorphine)
  - Schizophrenia (risperidone 6-month, ATI-9242)
- **Benefits of long-acting implants and injectables**
  - Improve patient outcomes
  - Improve public health
  - Decrease social cost outcomes associated with drug diversion, misuse and non-adherence

Challenges in the Opioid Addiction Field

- Opioid epidemic
- Perception of disease as a moral failing
- 30/100 patient limit
- Insurance coverage limitations
- Paucity of research and development of new treatments

Probuphine Regulatory Status

- **Two key issues identified by FDA in 2013 CRL**
  - Demonstration of clinical benefit in a specific population
  - Validation of training program
- **Stable patients on ≤8 mg SL BPN per day**
  - Good clinical sense
  - Probuphine delivers plasma concentrations approximating 4 to 8 mg per day of buprenorphine

Braeburn Investigational Products for Opioid Dependence

- **Early stage treatment**
  - Frequent visits, at least weekly
  - Dose titration
  - Higher level of blockade desired
  - Braeburn solution: CAM-2038 weekly injection, highly titratable
- **Maintenance treatment**
  - Monthly visits
  - Dose stabilized
  - Braeburn solutions: Probuphine six-month implant and CAM-2038 monthly injection

Probuphine® Implant

- **Each implant contains 80 mg of buprenorphine HCl, in EVA matrix**
- **4 implants inserted sub-dermally in the upper arm**
- **Continuous delivery over 6 months**
- **Studied in 647 subjects over the last 12 years**
- **Granted priority review by FDA in 2012**
  - Lower risk of diversion, misuse, and accidental pediatric exposure

Study PRO-814

- Collaboration with FDA and global addiction experts
- Novel, methodologically rigorous trial
- Strong results for SL BPN in the previously understudied stable population
- Non-inferiority demonstrated

Agenda

Introduction	**Behshad Sheldon** *President and CEO* *Braeburn Pharmaceuticals*
Public Health Need	**Frank E. Young, MD, PhD** *Executive Vice President Regulatory and Medical* *Braeburn Pharmaceuticals*
Medical Need	**Michelle Lofwall, MD** *Associate Professor* *University of Kentucky College of Medicine*
Efficacy	**Sonnie Kim, Pharm.D.** *Vice President, Clinical Development and Medical Affairs* *Braeburn Pharmaceuticals*
Training Program **Safety**	**Steve Chavoustie, M.D., FACOG** *Principal Investigator, Segal Institute for Clinical Research* *Volunteer Assistant Professor, University of Miami, Miller School of Medicine*
Risk Management	**Behshad Sheldon** *President and CEO* *Braeburn Pharmaceuticals*
Benefit/Risk	**Michael P. Frost MD, FACP, FASAM** *Medical Director, Eagleville Hospital* *President, Frost Medical Group*

Public Health Challenge of Opioid Dependence

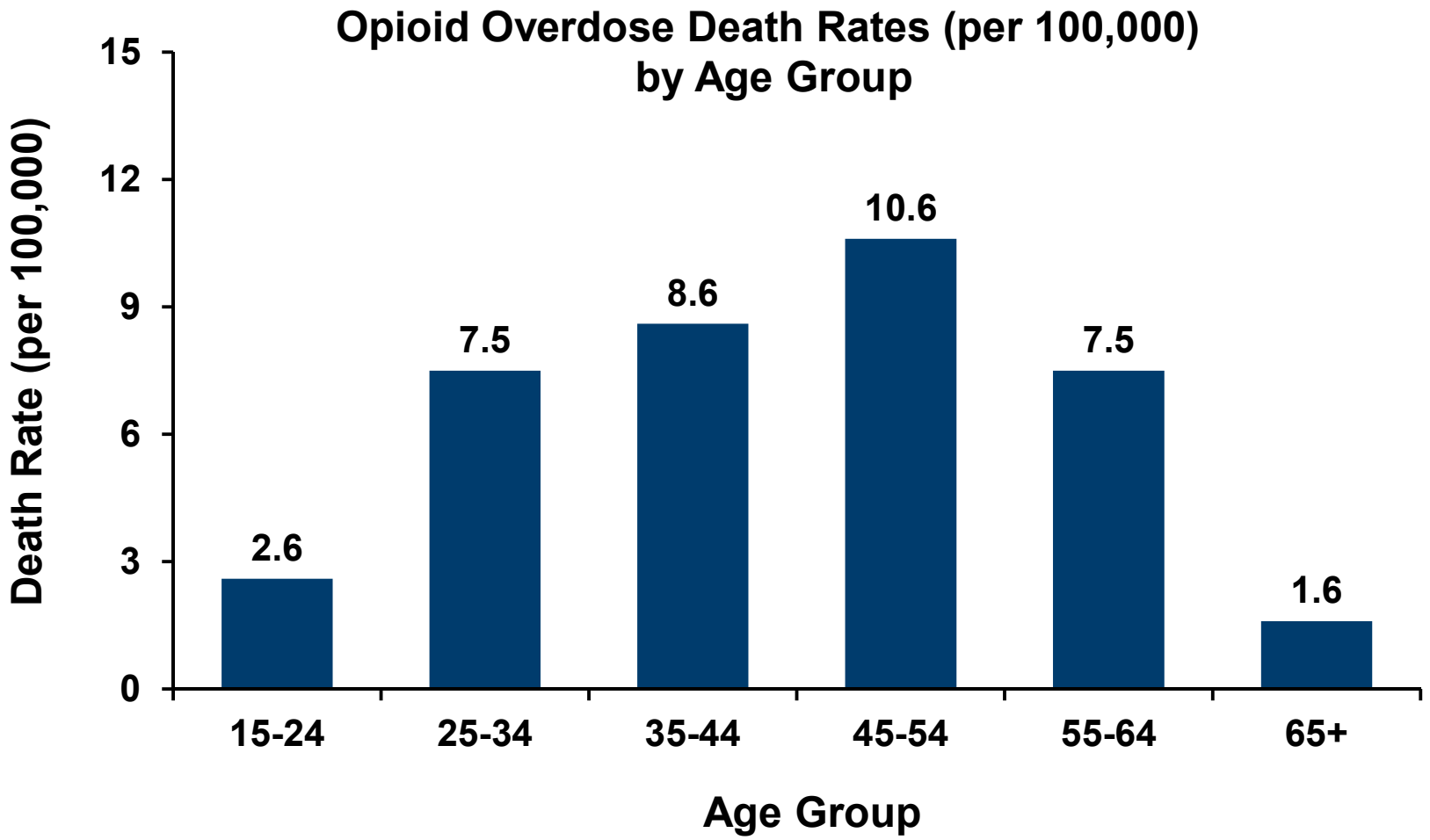
Frank E. Young, MD, PhD

Executive Vice President Regulatory and Medical
Braeburn Pharmaceuticals, Inc.

Opioid Abuse Epidemiology

- 4.3 million Americans abuse opioids each year
- 2.4 million Americans are dependent on opioids
- Over 26,000 Americans died from opioid-related overdoses in 2014
- Prescription opioid-related deaths in the U.S. increased by 9% between 2013 and 2014
- Heroin-related overdose deaths in the U.S. more than tripled between 2010 and 2014

Prescription Opioid Overdose Deaths 1999-2013 by Age



http://www.cdc.gov/drugoverdose/data/overdose.html

Medical Need

Michelle Lofwall, MD

Associate Professor
Departments of Behavioral Science & Psychiatry
Center on Drug and Alcohol Research
University of Kentucky College of Medicine

Barriers to Treatment

- **Long wait to initiate treatment**
- **Few medication options**
- **Medication diversion is an important issue**
  - 7-fold increased risk if they failed to access treatment[1]
  - Consistent with other studies reporting use of diverted BPN for self-treatment of addiction[2]
- **Finding novel medications that minimize diversion risk and expand treatment access may be one of the most effective public health strategies**

[1] Lofwall and Havens *Drug Alcohol Depend,* 2012.
[2] For review see: Lofwall and Walsh, *J Addict Med,* 2014.

Needs and Challenges During Treatment

- Psychosocial problems
- Comorbid psychiatric and medical disorders
- Criminal justice challenges
- Many with fewer comorbidities

Stable Patient Characteristics

- **No clear definition in literature**
- **Stable does not mean perfect**
- **General characteristics**
  - Low rate of positive urine tests
  - Regular clinic visits – adherent to treatment plan
  - Improved psychosocial function
  - Consistent doses of BPN although dose adjustment still possible

Challenges for Stable Patients

Challenges for Stable Patients

Adherence

Challenges for Stable Patients

Adherence

Confidentiality and Stigmatization

Challenges for Stable Patients

Confidentiality and Stigmatization

Conclusions

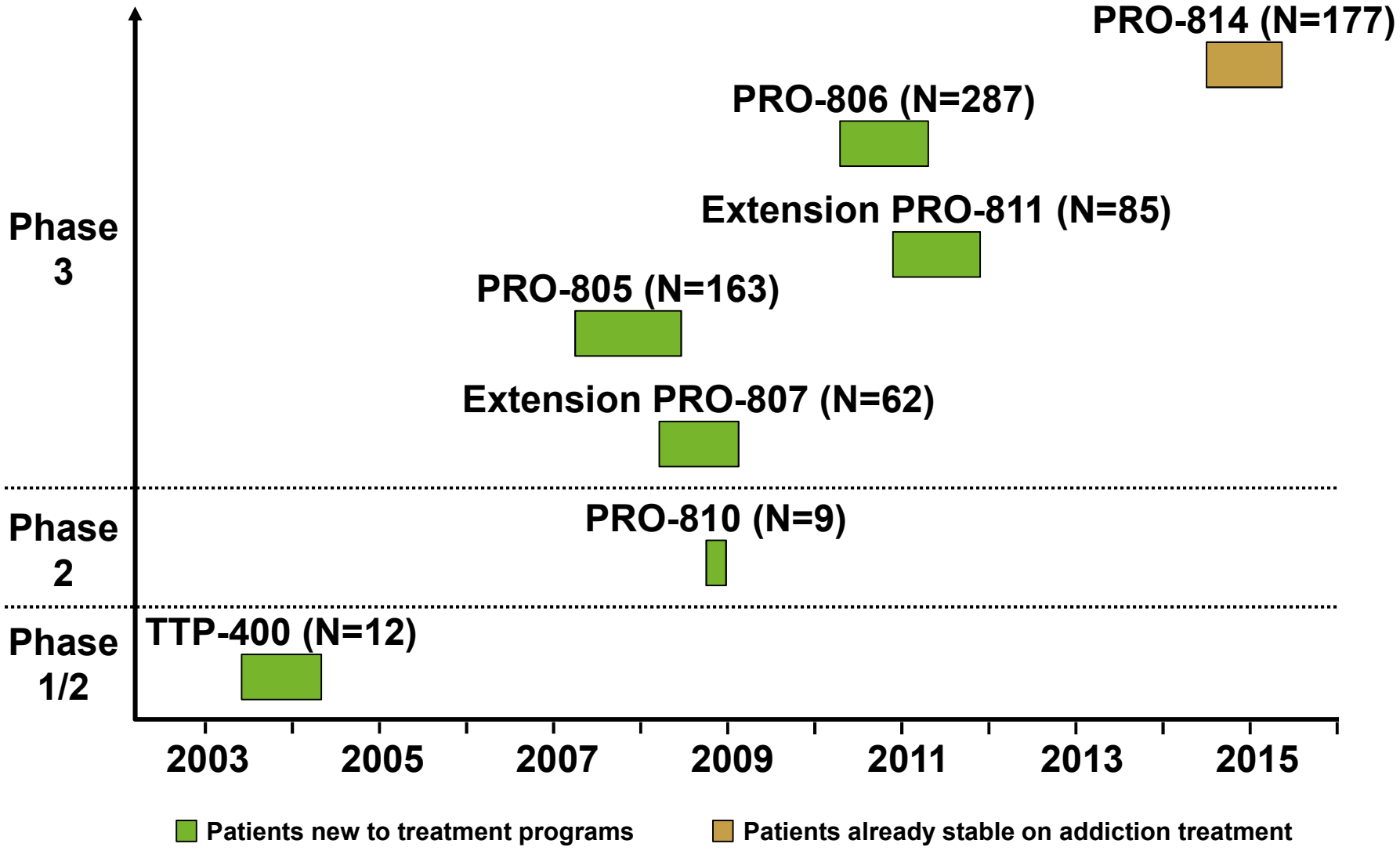
- **Stable patients work hard to be in treatment**
- **Patients want**
  - Convenient and confidential treatment
  - Reliable medication
- **Providers and public want**
  - Less diversion and misuse
  - Less unintentional pediatric exposures
- **Implantable buprenorphine meets these needs**

Probuphine Efficacy

Sonnie Kim, Pharm.D.

Vice President, Clinical Development and Medical Affairs

Probuphine Clinical Program



Defining Patient Population for PRO-814

- **Considered clinically stable by their treating healthcare provider, confirmed by following at randomization**
  - Had been on SL BPN treatment for 6 months
  - Had been on a SL BPN dose of ≤8 mg/day for at least the last 90 days
  - Had no positive urine toxicology results for illicit opioids in the last 90 days
- **Free from significant withdrawal symptoms measured at screening**
  - COWS score ≤5

Physician Attestation of Clinical Stability

- **Treating physician to attest to the clinical stability of the patient**
- **Based on clinical judgment considering the following:**
  - Stable living environment
  - Participation in structured activity/job
  - Consistent participation in cognitive therapy or peer support
  - Consistently compliant with clinic visits
  - No reported desire or need to use illicit opioids in past 90 days
  - No hospitalizations (for addiction or mental health issues), ER visits, or crisis interventions in past 90 days

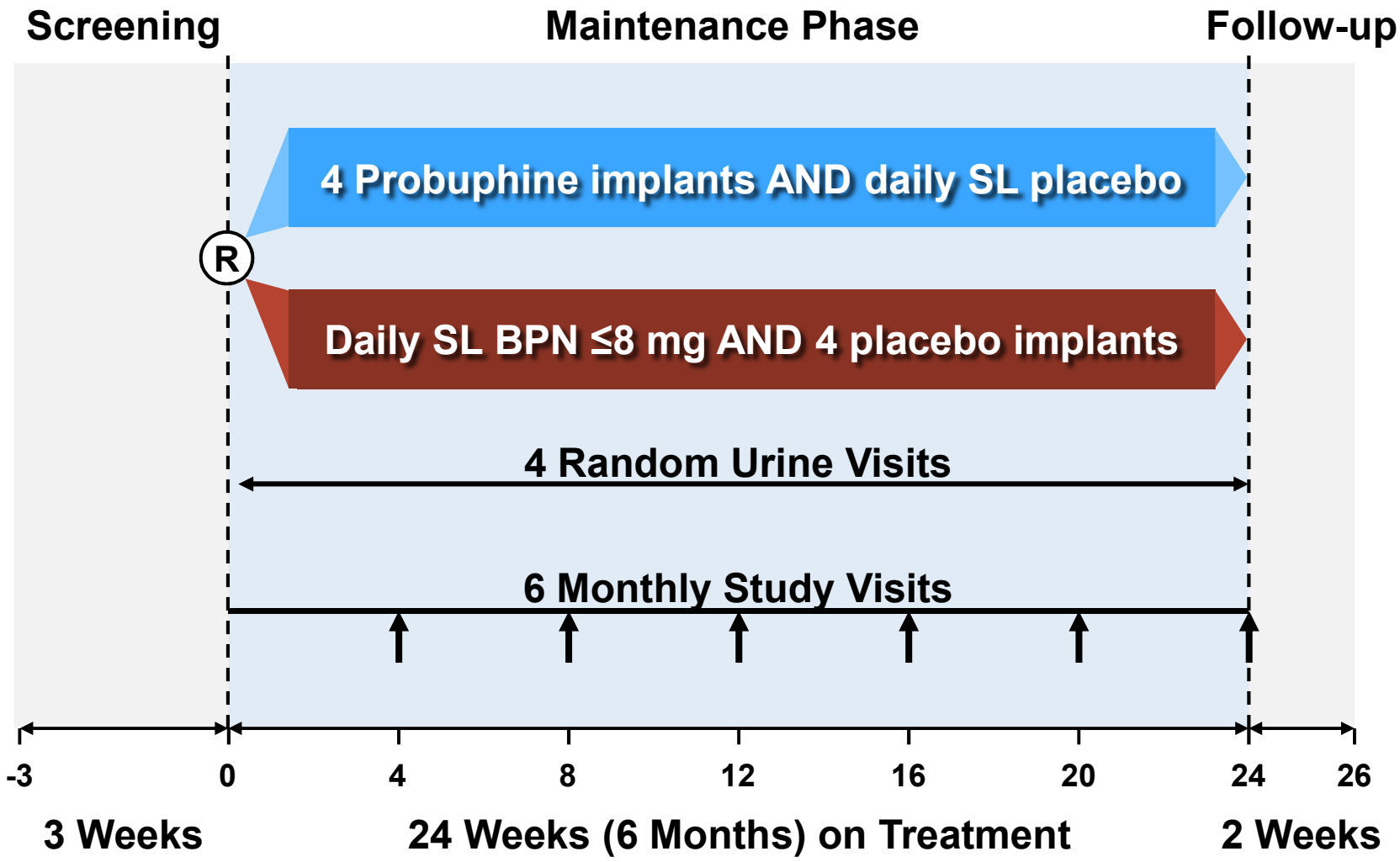
Choice of Non-inferiority Trial

- **Placebo-controlled study unethical for stable patients**
  - The vast majority of stable patients relapse when removed from maintenance therapy
- **Non-inferiority design with active control comparison clinically appropriate and feasible**
  - Double-blind, double-dummy, non-inferiority design
  - Non-inferiority margin of 20%
    - Supported by literature and addiction expert survey

Selection of Non-inferiority Margin

- **Innovative approach in addiction treatment trials**
- **Input of addiction experts and literature review**
- **Estimated effect size of SL BPN versus placebo in stable patients ~75%**
- **FDA guidance: Preserve 50% of effect size**
  - 37.5% NI Margin
- **More conservatively preserve >70% of effect size**
  - 20% NI Margin

Study Design
PRO-814



CE-28

Quantitative Analysis of Urine Toxicology

- **Liquid chromatography tandem mass spectrometry [LC-MS/MS]**
- **Very low limit of quantification for opioids tested**
  - 50 ng/mL for codeine, morphine, dihydrocodone, hydrocodone, hydromorphone, oxycodone, and oxymorphone
  - 200 ng/mL for methadone and EDDP (metabolite of methadone)
  - 1.0 ng/mL for fentanyl and norfentanyl (metabolite of fentanyl)

Demographics
Safety Dataset

Characteristic	Probuphine N=87	SL BPN N=89	Total N=176
Mean age, y	**38 ± 11.2**	**39 ± 10.8**	**39 ± 11.0**
Sex, %			
Male	58.4	59.8	59.1
Female	41.6	40.2	40.9
Race, %			
White	94.3	95.5	94.9
Black or African American	3.4	2.2	2.8
Asian	1.1	0.0	0.6
American Indian or Alaska Native	1.1	1.1	1.1
Other	0.0	1.1	0.6
Ethnicity, %			
Hispanic or Latino	3.4	3.4	3.4
Not Hispanic or Latino	96.6	96.6	96.6
Highest educational level achieved, %†			
Less than high school or other training	19.5	22.5	21.0
GED/high school diploma	56.3	51.7	54.0
4-year college degree or higher	24.1	25.8	25.0
Current employment status %†			
Full time (35+ hours weekly)	59.8	50.6	55.1
Part time	5.7	13.5	9.7
Unemployed	17.2	19.1	18.2
Student, retired/disability, homemaker	17.2	16.9	17.0

† Data reported for the safety population; all other data is from the intent-to-treat population.

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Highest educational level achieved, %†			
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GED/high school diploma	56.3	51.7	54.0
4-year college degree or higher	24.1	25.8	25.0
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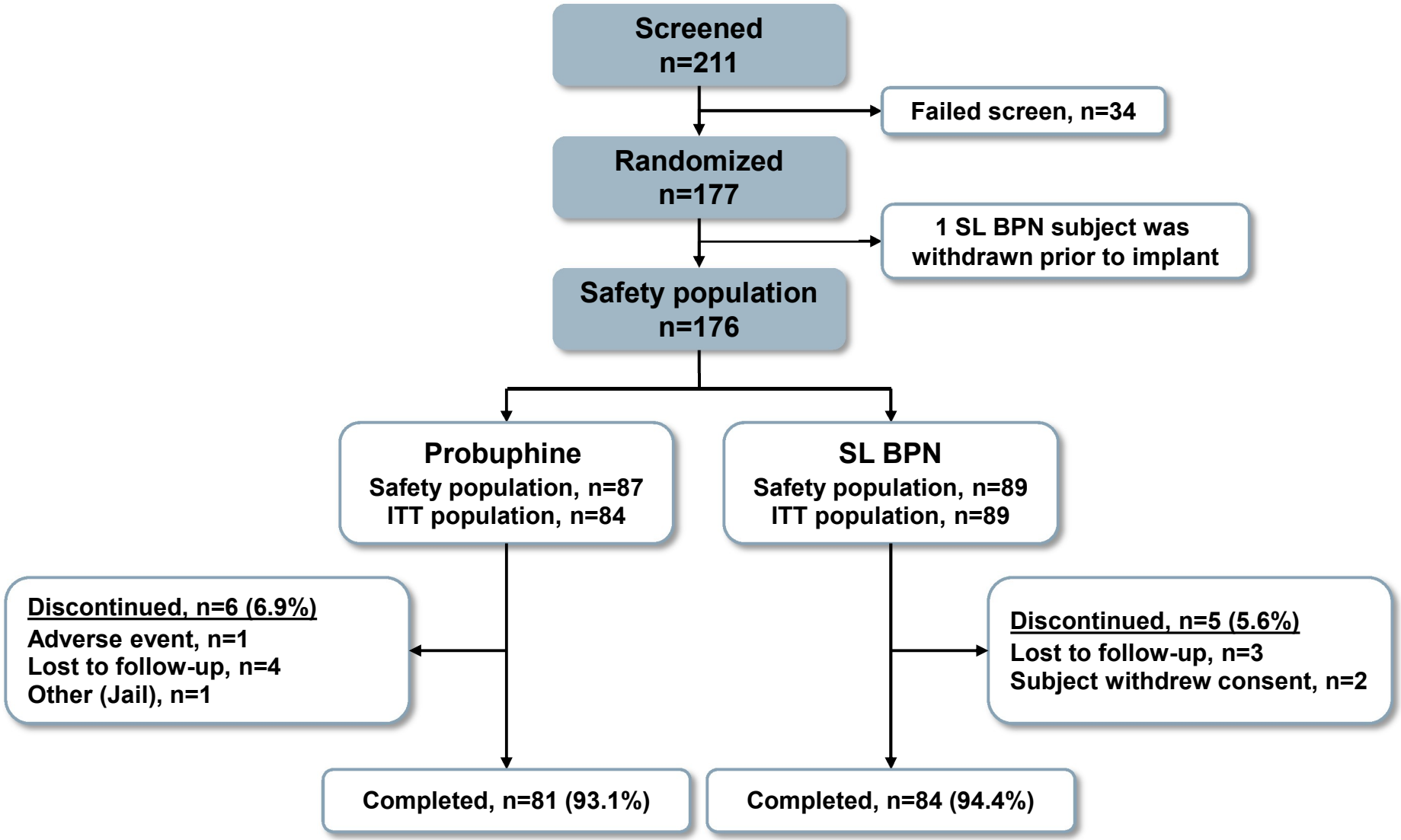
Baseline Disease Characteristics
Safety Dataset

Characteristic	Probuphine N=87	SL BPN N=89	Total N=176
Primary opioid of abuse, %			
Prescription opioid pain reliever	75.9	73.0	74.4
Heroin	17.2	24.7	21.0
Both	5.7	2.2	4.0
Not reported	1.1	0	0.6
Time since first opioid abuse (years)			
Mean	11.2	11.5	11.3
Time since first diagnosis (years)			
Mean	6.2	6.2	6.2
Buprenorphine treatment (years)			
Mean	3.5	3.4	3.5
Dose of Buprenorphine at study entry (mg/day), %			
2	6.9	3.4	5.1
4	13.8	16.9	15.3
6	9.2	4.5	6.8
8	70.1	75.3	72.7

Enrollment and Subject Disposition



Primary Efficacy Analysis

- **Primary efficacy analysis was the difference of responder rates at Week 24 between Probuphine and SL BPN**
- **Responder defined as a subject with 4 out of 6 months without any evidence of illicit opioid use**
- **Each month window was assessed for evidence of positive illicit opioid use by:**
  - A positive opioid urine toxicology result for scheduled monthly visit; or
  - Self-reported illicit opioid use; or
  - A positive opioid urine toxicology results for random urine sample if collected during the month window
- **Self-reported illicit opioid use was considered evidence of illicit opioid use regardless of urine toxicology results**

Illustration of Non-inferiority

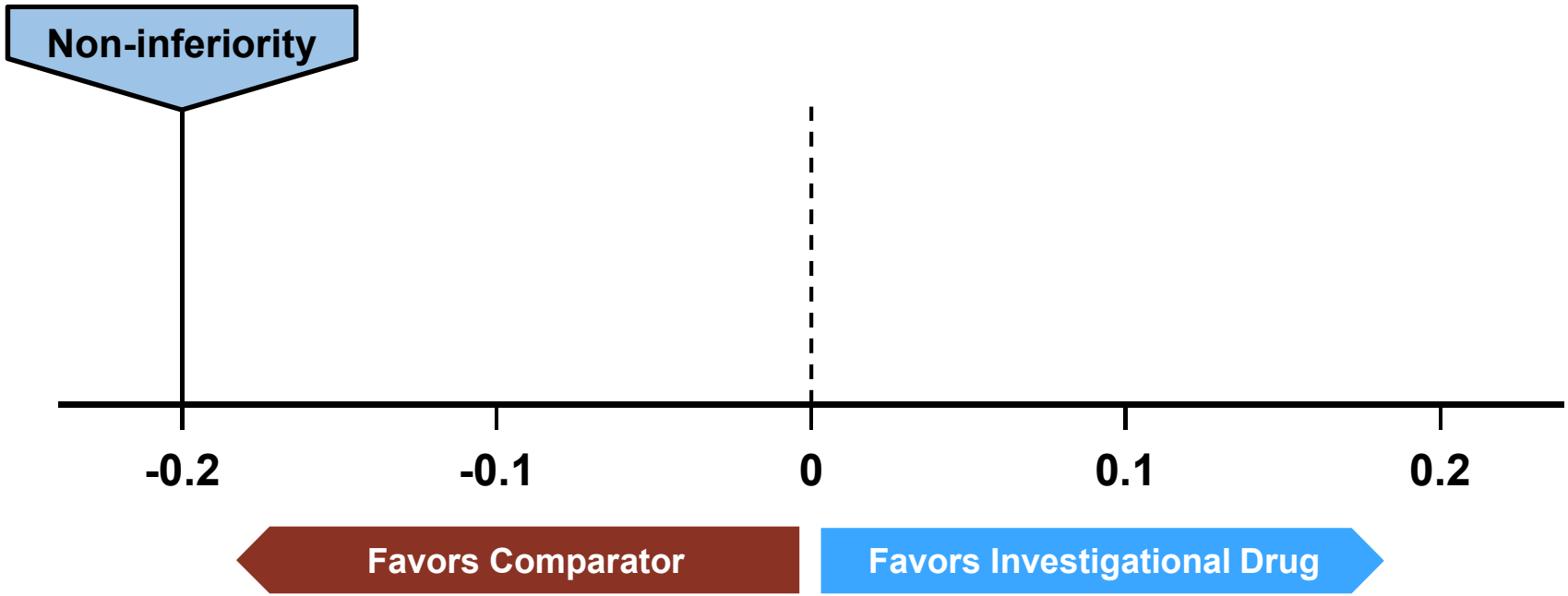


Illustration of Non-inferiority

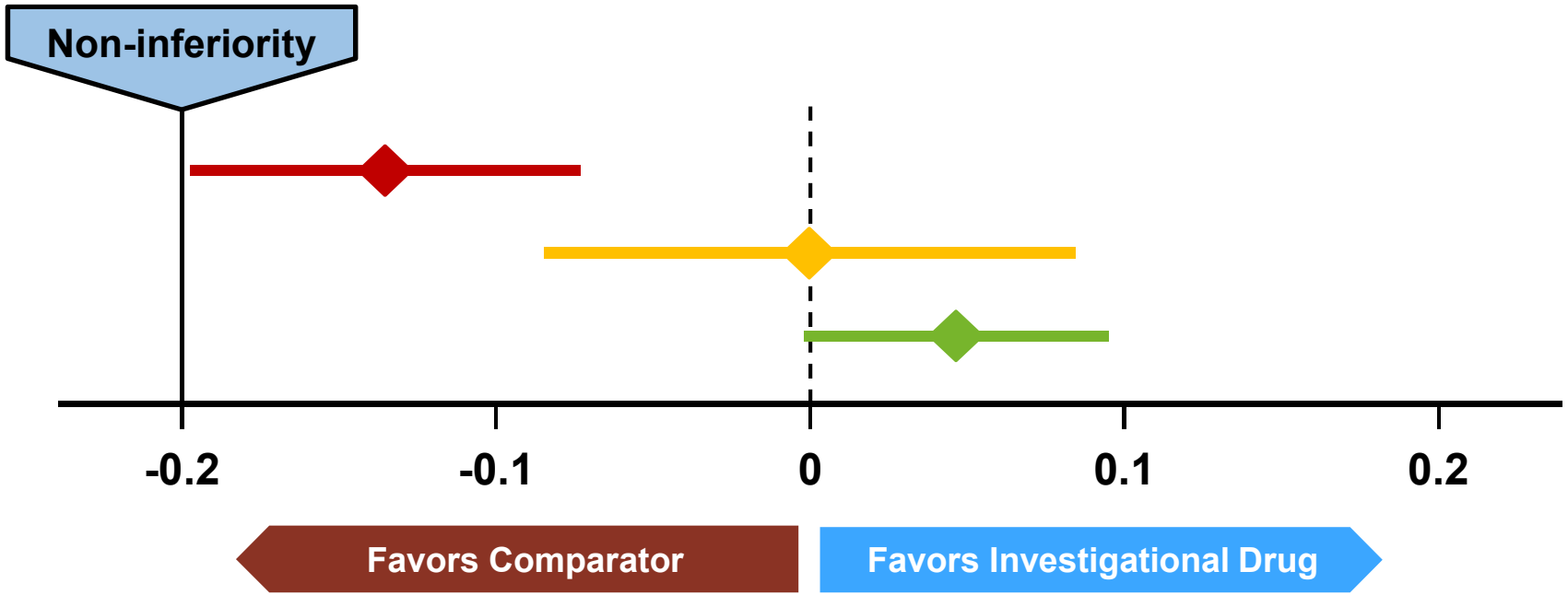
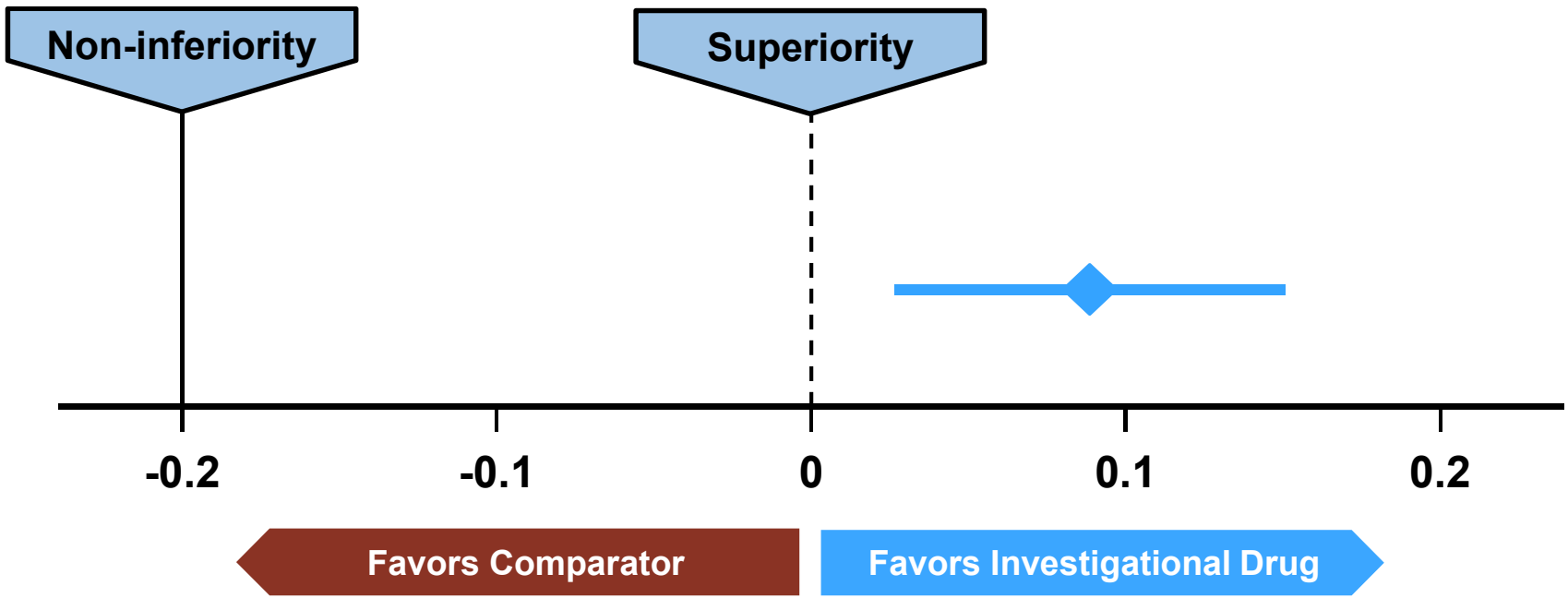
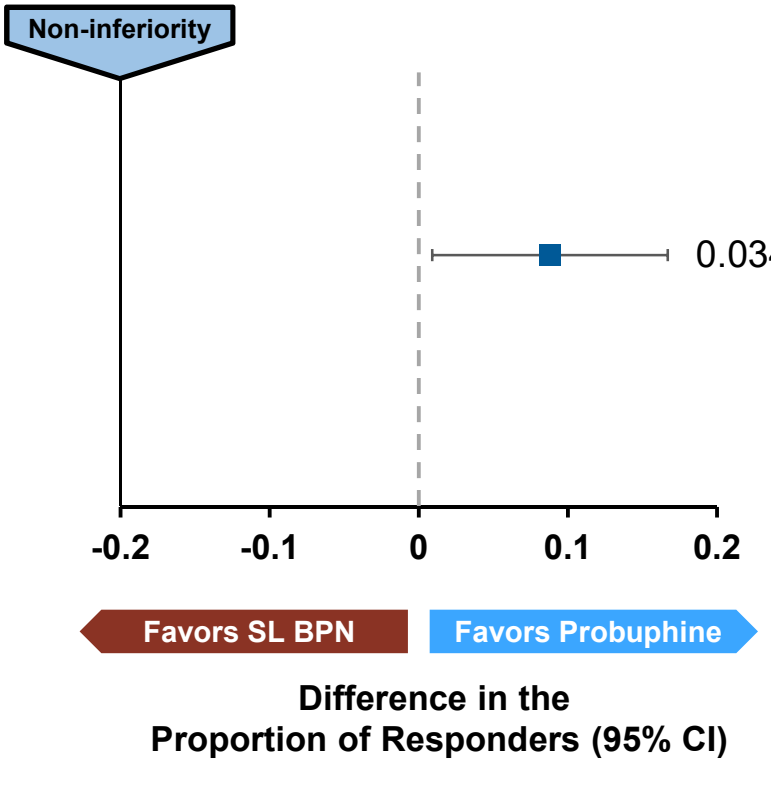


Illustration of Superiority



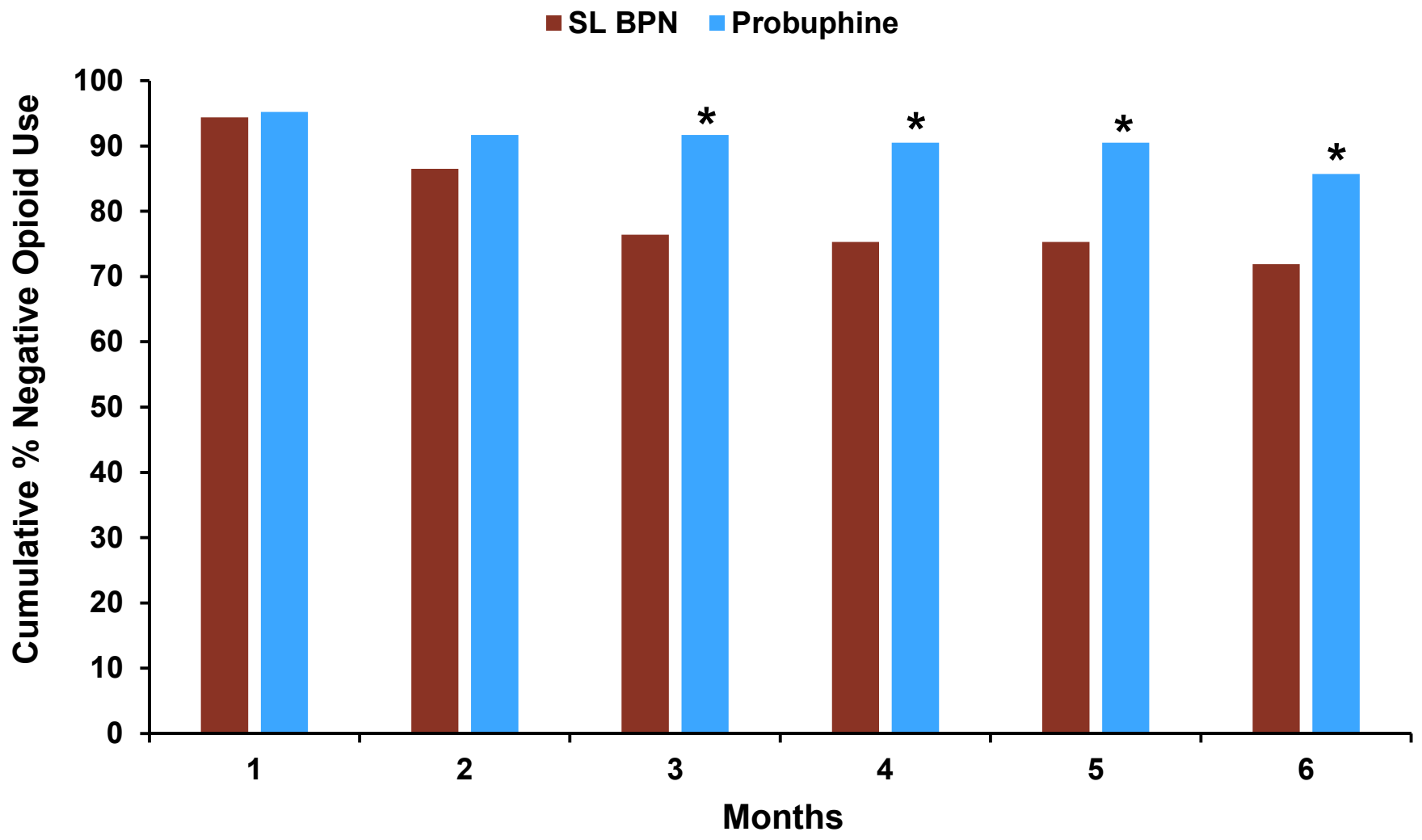
Primary Endpoint: Responder Rates
ITT Dataset

Proportion of Responders	SL BPN n/N (%)	Probuphine n/N (%)	p-value (2-Sided)
Primary Endpoint: Primary Imputation ITT	78/89 (87.6)	81/84 (96.4)	0.034



Secondary Endpoint: Cumulative Percentage of Subjects with No Illicit Opioid Use by Month

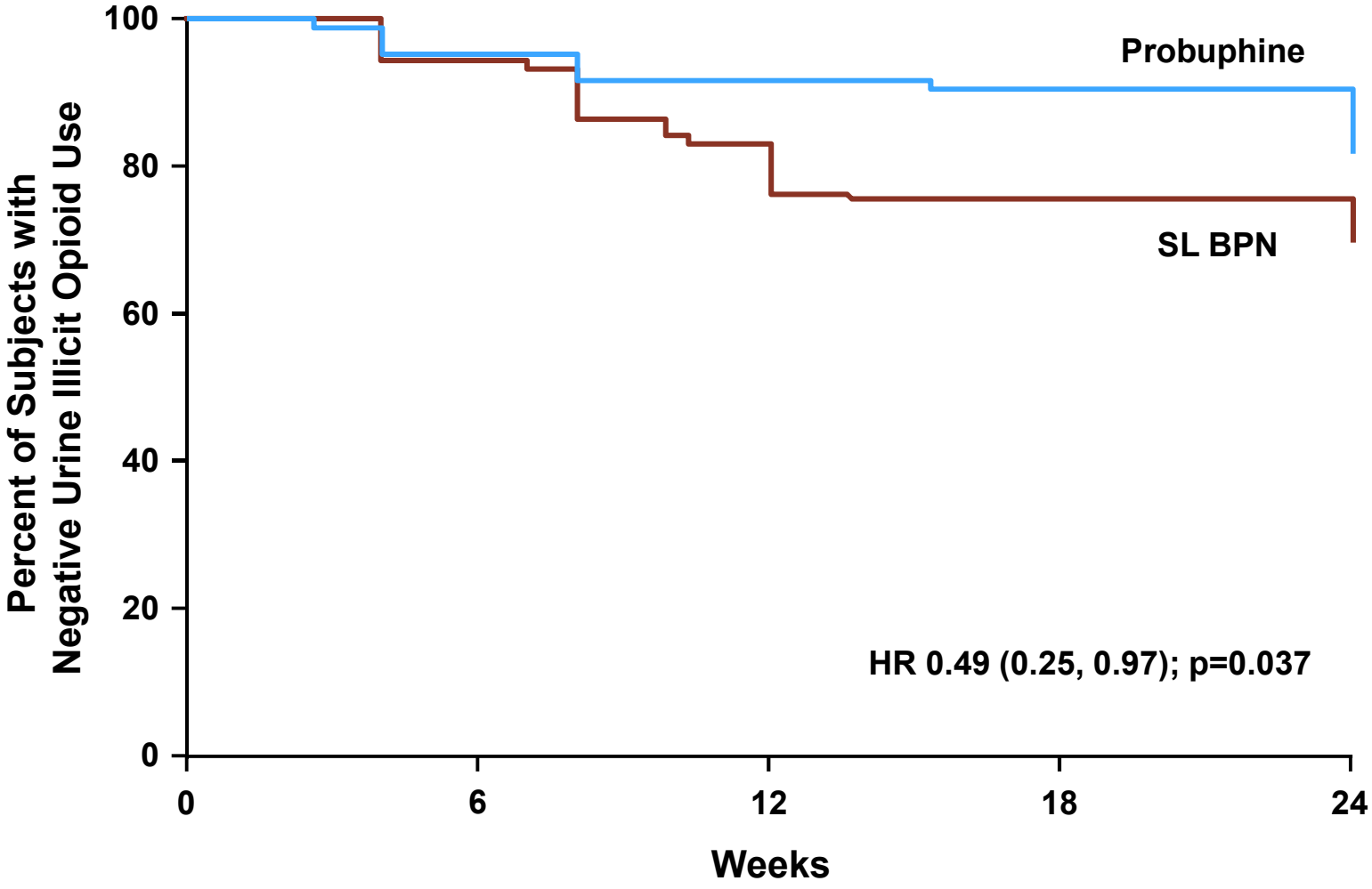
ITT Dataset



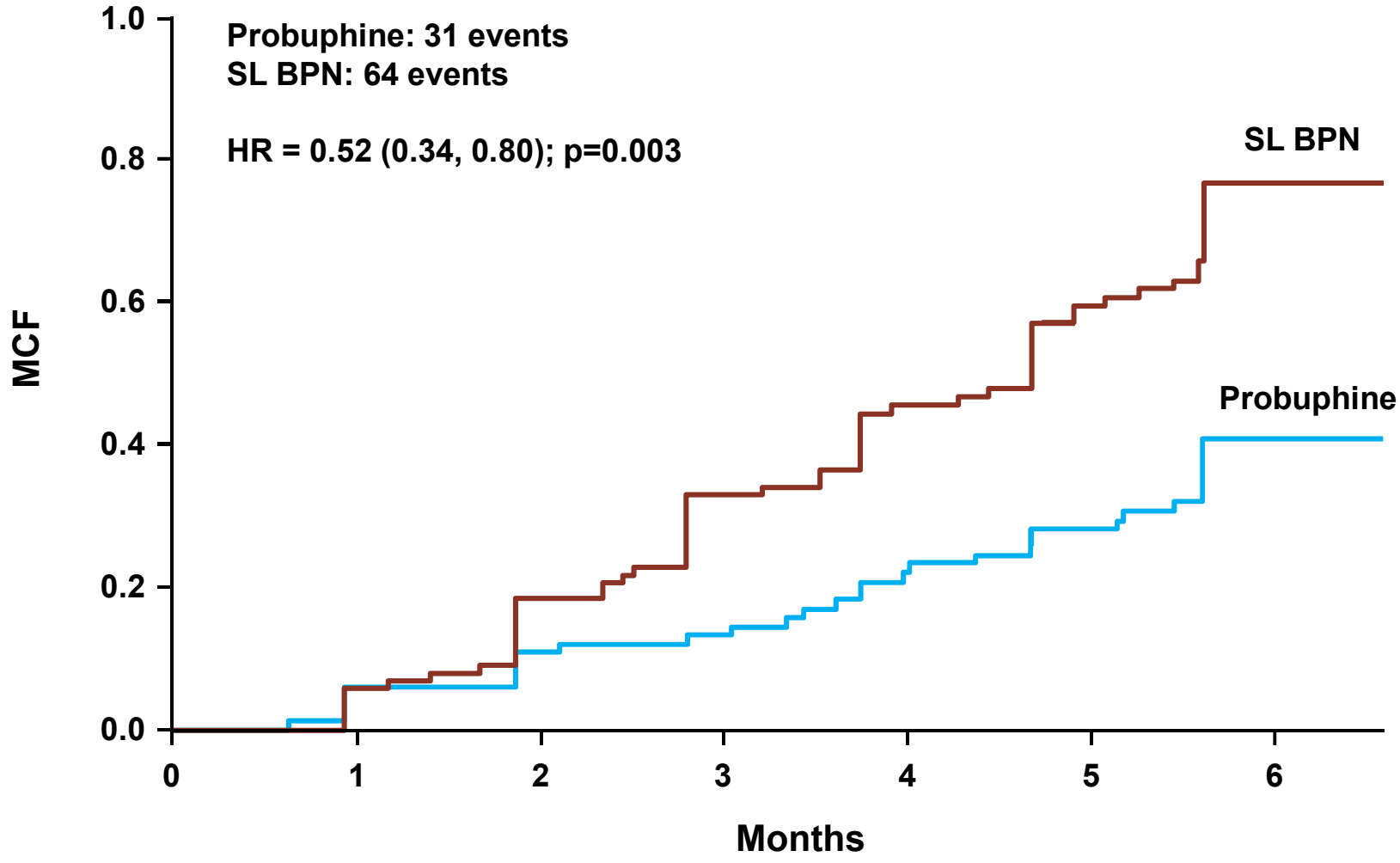
* p<0.05

Secondary Endpoint: Time to First Evidence of Illicit Opioid Use by Urine Toxicology

PRO-814 – ITT Population

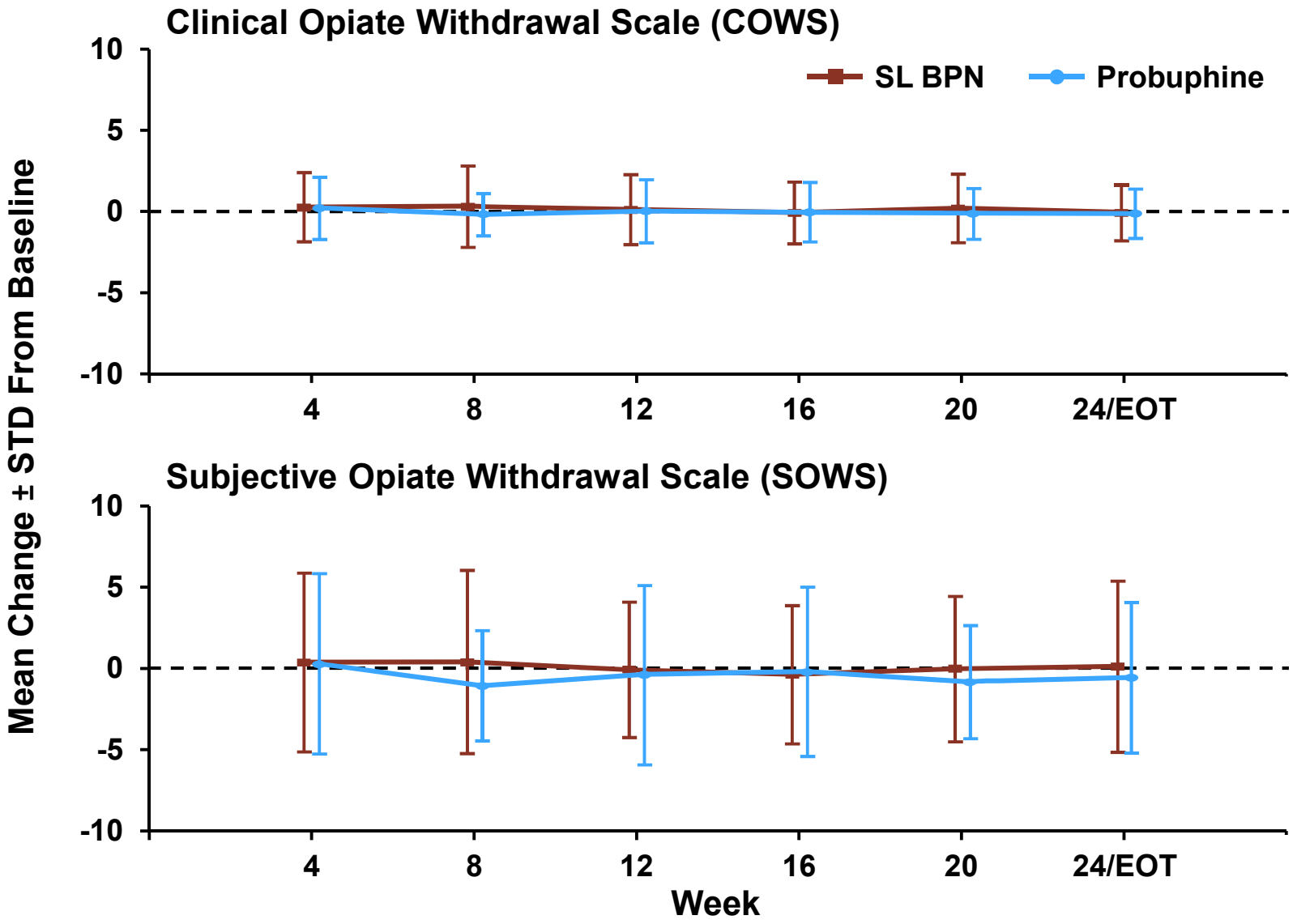


Number of Events of Illicit Opioid Use



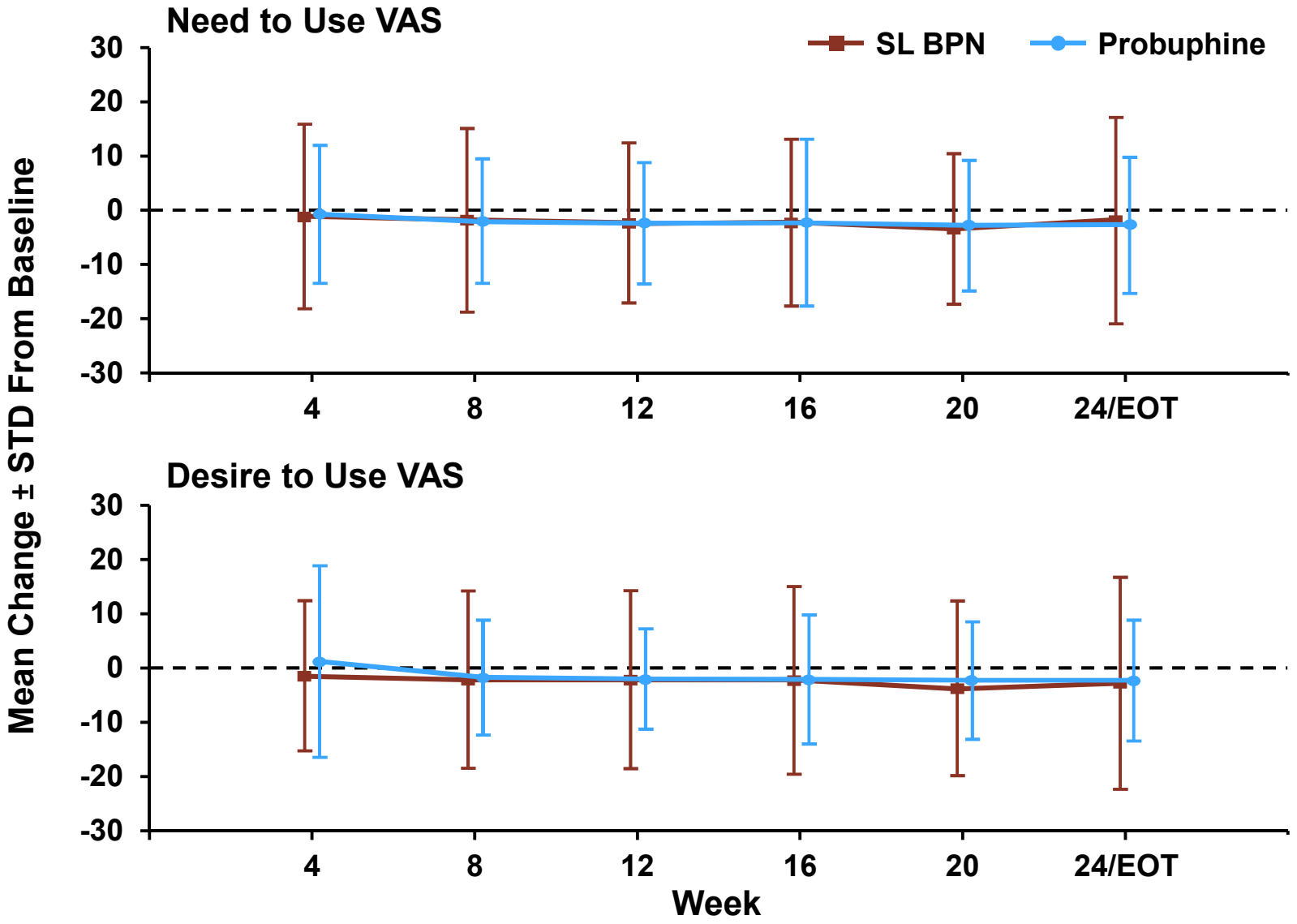
Opioid Withdrawal Measured by COWS and SOWS

PRO 814 – ITT Population



Control of Craving Measured by Need and Desire to Use Opioid

PRO 814 – ITT Population

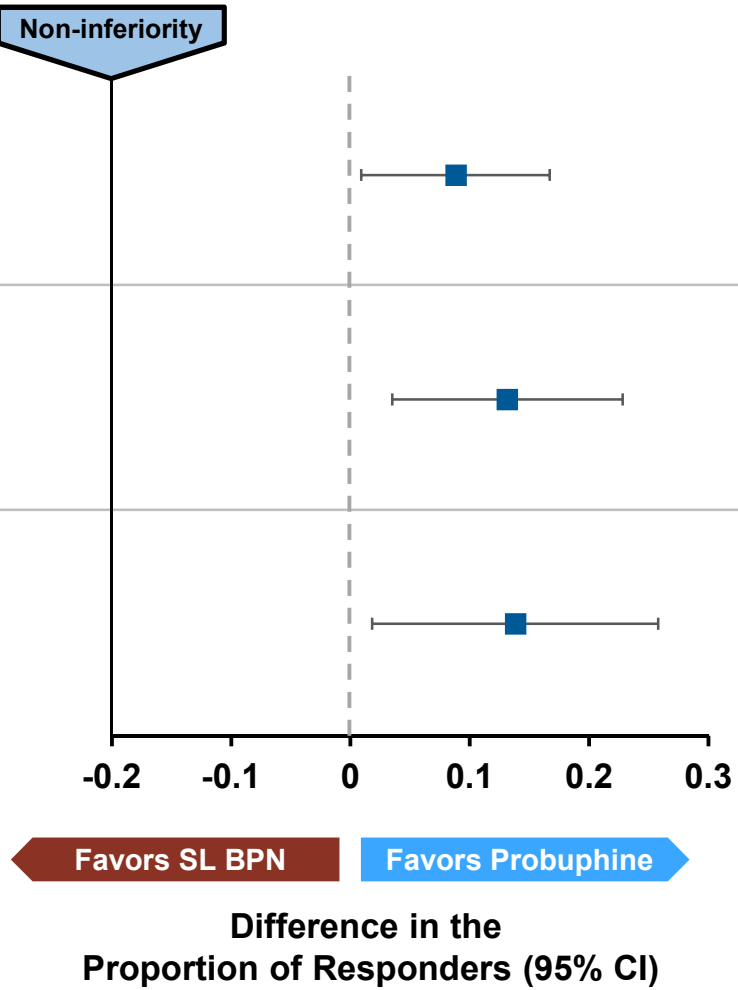


Sensitivity Analyses

Primary Endpoint Based on Conservative Responder Definitions (5/6 and 6/6 Months no Evidence of Opioid)

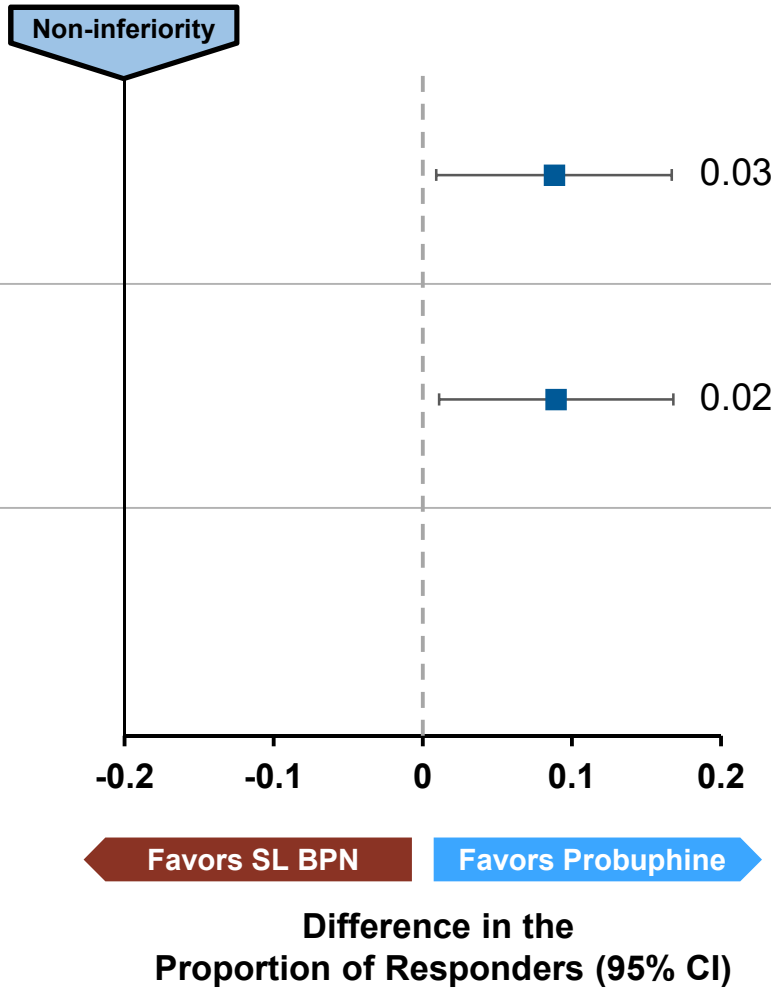
ITT Dataset

	SL BPN n/N (%)	Probuphine n/N (%)	p-value (2-Sided)
Primary Endpoint: 4 months no evidence of opioid use	78/89 (87.6)	81/84 (96.4)	0.034
Sensitivity Analysis: 5 months no evidence of opioid use	72/89 (80.9)	79/84 (94.0)	0.009
Sensitivity Analysis: All 6 months no evidence of opioid use	64/89 (71.9)	72/84 (85.7)	0.027



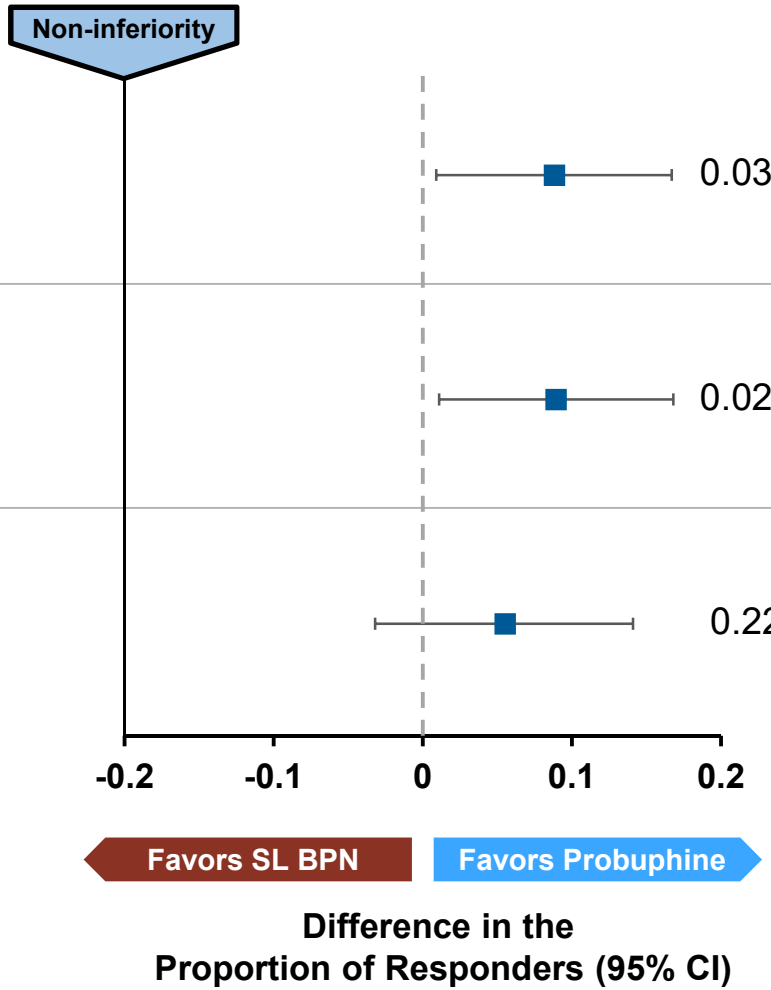
Primary Endpoint Based on Analysis Datasets

Sensitivity Analyses for Proportion of Responders	SL BPN n/N (%)	Probuphine n/N (%)	p-value (2-Sided)
Primary Endpoint ITT Population (SAP) Primary imputation	78/89 (87.6)	81/84 (96.4)	0.034
Primary Endpoint FDA ITT Population (Protocol) Primary imputation	78/89 (87.6)	84/87 (96.6)	0.029



Primary Endpoint Based on Analysis Datasets

Sensitivity Analyses for Proportion of Responders	SL BPN n/N (%)	Probuphine n/N (%)	p-value (2-Sided)
Primary Endpoint **ITT Population (SAP)** **Primary imputation**	78/89 (87.6)	81/84 (96.4)	0.034
Primary Endpoint **FDA ITT Population (Protocol)** **Primary imputation**	78/89 (87.6)	84/87 (96.6)	0.029
Primary Endpoint **FDA ITT Population (Protocol)** **Imputation of 3 Subjects as Non-responder**	78/89 (88)	81/87 (93)	0.22



Missing Urine Samples: Primary Imputation Methods

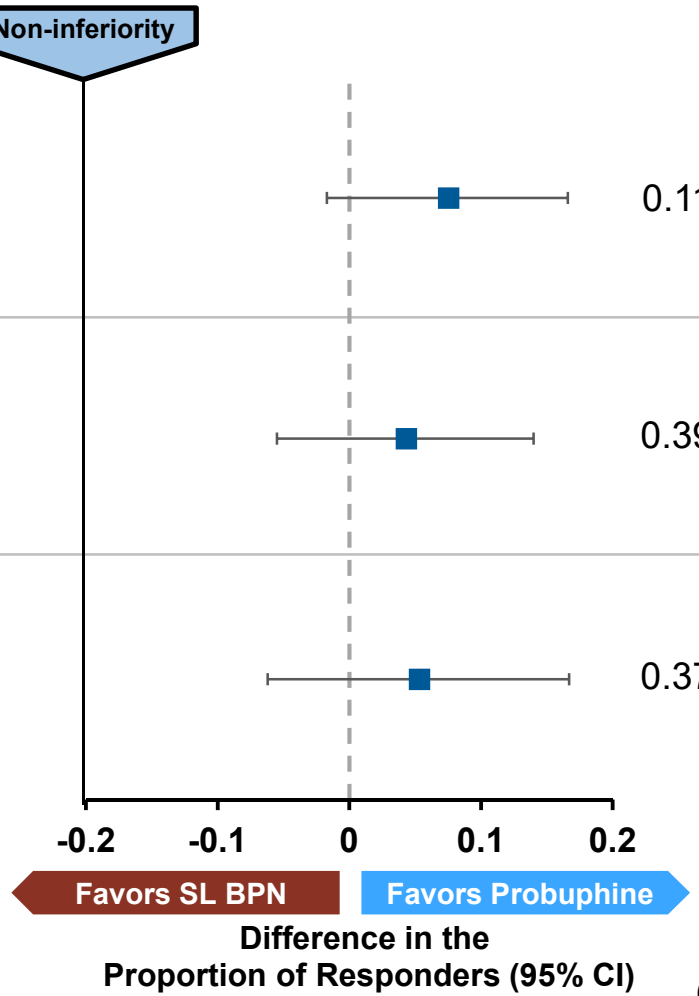
- **Imputation of missing data in SL BPN group:**
  - Calculate percentage of positive urine sample for each subject
  - Using patient level proportions, calculate average proportion of positive urine for SL BPN group
  - This average proportion = group specific probability of positive urine tox
- **Imputation of missing data in Probuphine group:**
  - Same as above, determine average proportion for SL BPN and Probuphine group specific probability of positive urine tox
  - Determine which group has the highest probability
  - Use this probability and add 20% (multiply by 1.2)

Missing Urine Samples and Incomplete Urine Panel Items

	Probuphine	Total	SL BPN	Total
Missing samples	24/840	3%	27/890	3%
Missed scheduled samples	11/504	2%	12/534	2%
Missed random sample	13/336	4%	15/356	4%
Refused by patient	0/504	0%	1/534	0.2%
Number of incomplete individual panel items	277/18,480	1.5%	318/19,580	1.6%
Creatinine issue	7/816	0.9%	10/863	1.2%
Out of stability window (>1 wk)	3/816	0.4%	2/863	0.2%
Samples with incomplete panel items	60/816	7%	34/863	4%

Primary Endpoint Based on Missing Data Imputations

Sensitivity Analyses for Proportion of Responders	SL BPN n/N (%)	Probuphine n/N (%)	p-value
Missing urine samples imputed as positive (ITT Dataset)	76/89 (85.4)	78/84 (92.9)	0.117
Missing urine samples imputed as positive (ITT Dataset with 3 Subjects)	76/89 (85.4)	78/87 (89.7)	0.393
Missing urine panel items AND missing urine samples imputed as positive (ITT Dataset with 3 Subjects)	70/89 (78.7)	73/87 (83.9)	0.372



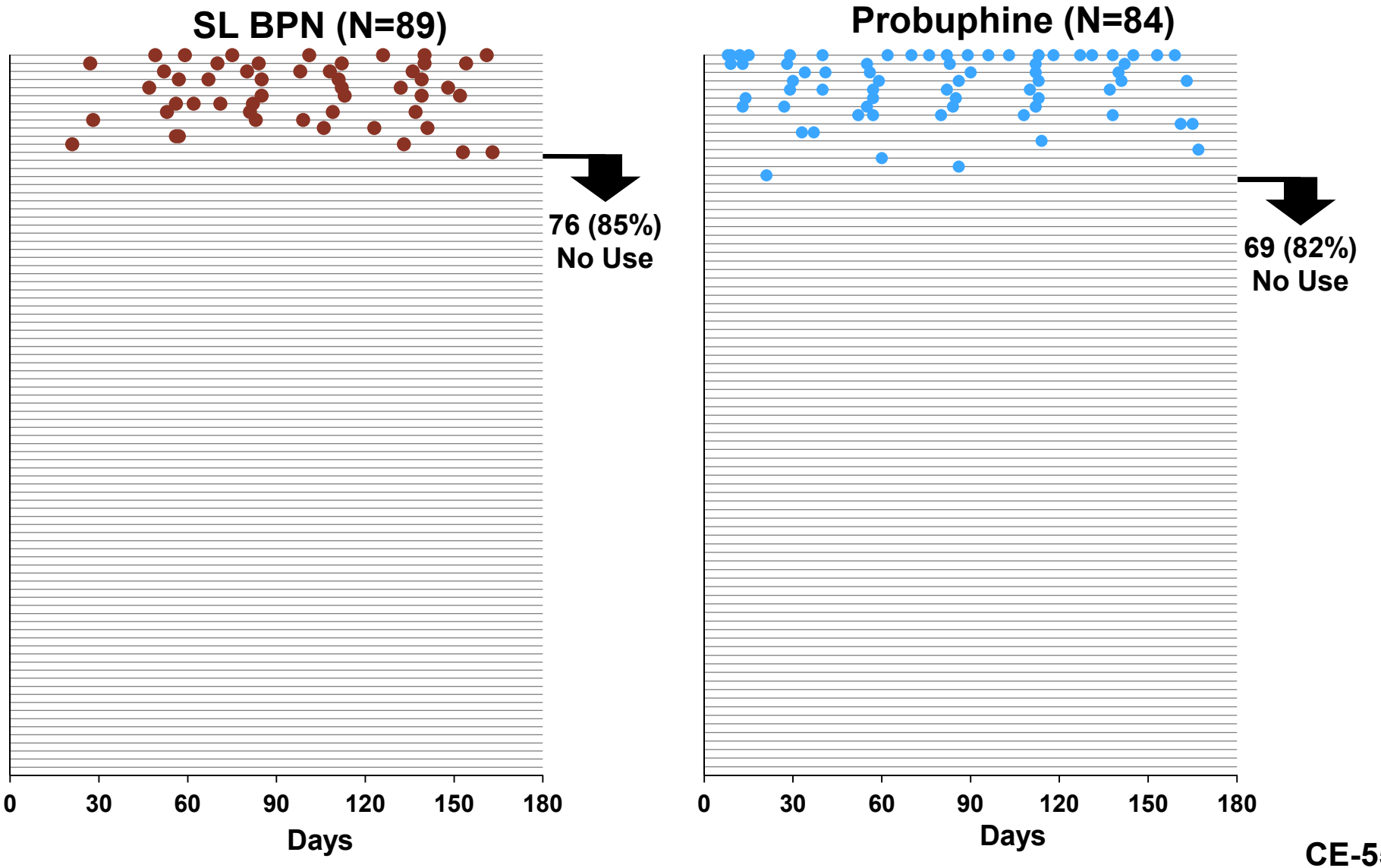
Supplemental SL BPN Use

ITT Dataset

	Dispensing Episodes	Probuphine N=84	SL BPN N=89
Number of subjects who were dispensed supplemental SL BPN		**15**	**13**
	1	5	0
	2	2	3
	3	0	2
	4	1	4
	5	2	2
	6	3	1
	7	1	1
	21	1	0

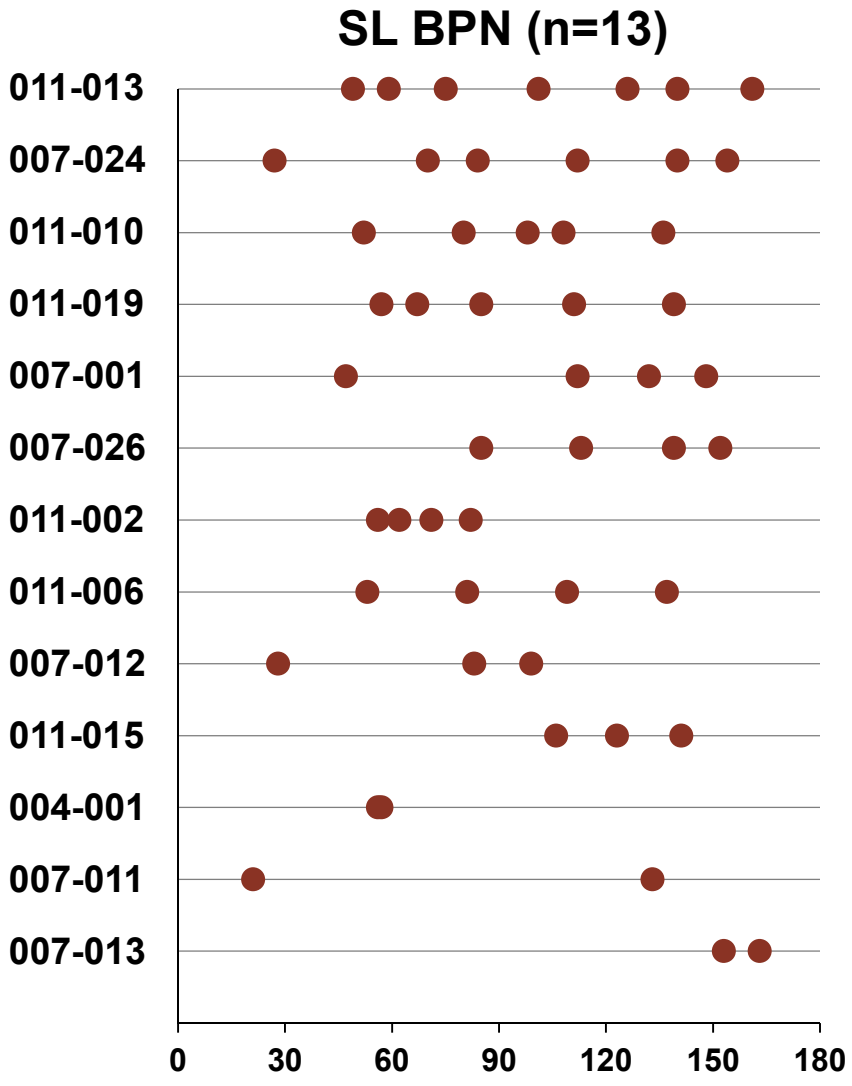
Supplemental BPN Use: All Subjects

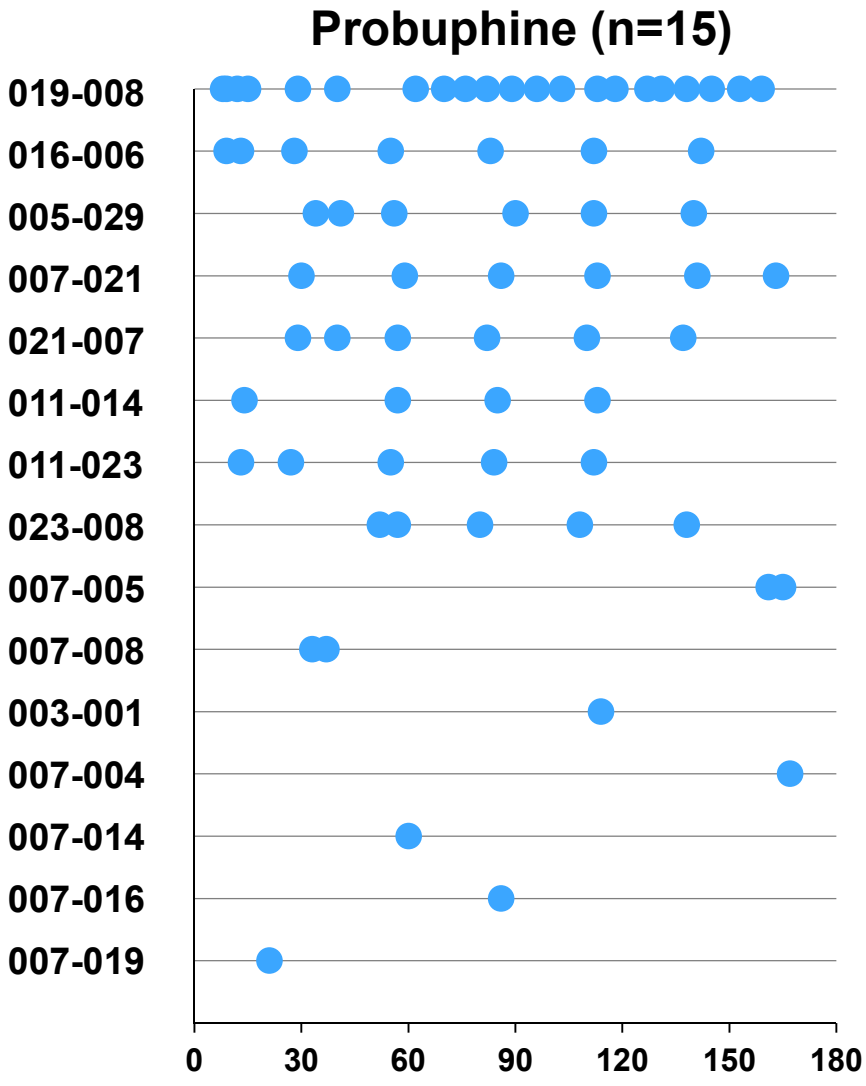
PRO-814



Subjects Who Used Supplemental BPN

PRO-814





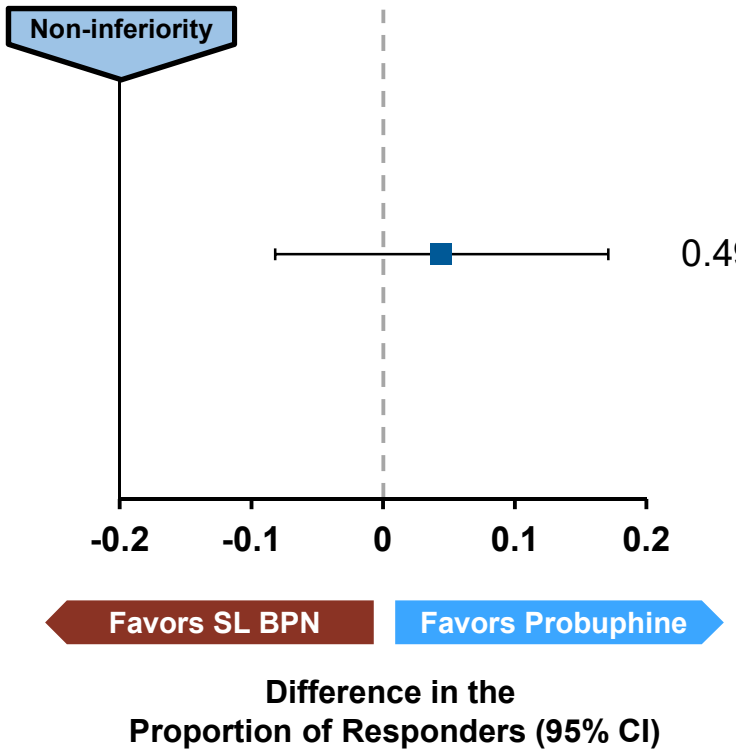
CE-56

Characterization of Subjects Who Took Supplemental BPN

Outcomes	Probuphine N=15 n (%)	SL BPN N=13 n (%)
Primary analysis response	**15 (100)**	**12 (92)**
6 months free of illicit opioid use	**13 (87)**	**9 (69)**
Prior dose of SL BPN at enrollment		
8 mg	12 (80)	10 (77)
6 mg	1 (7)	0
4 mg	2 (13)	3 (23)
2 mg	0	0
Missing urine samples	**2 (2 subjects)**	**5 (1 subject)**
Missing panel items	**3 samples (2 subjects)**	**--**

Primary Endpoint Based on Supplemental SL BPN Use

Sensitivity Analyses for Proportion of Responders	SL BPN n/N (%)	Probuphine n/N (%)	p-value
Primary Endpoint with supplemental SL BPN imputed as non-responders (ITT dataset)	66/89 (74.2)	66/84 (78.6)	0.495



Efficacy Conclusions

- The primary analysis met criteria for non-inferiority with a 95% CI of (0.009, 0.167)
- Moreover, the results favored Probuphine (p=0.034)
- Major secondary endpoint analysis results strongly support primary finding
- Totality of evidence supports the benefit of Probuphine
- Sensitivity analyses demonstrate robustness of results

Probuphine Insertion and Removal: Training and Safety During Clinical Studies

Steve Chavoustie, M.D., FACOG

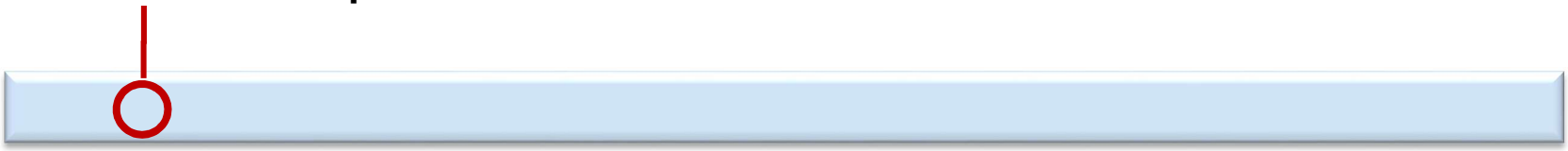
Principal Investigator
Segal Institute for Clinical Research

Volunteer Assistant Professor
Obstetrics and Gynecology, Family Medicine and Community Health University of Miami, Miller School of Medicine

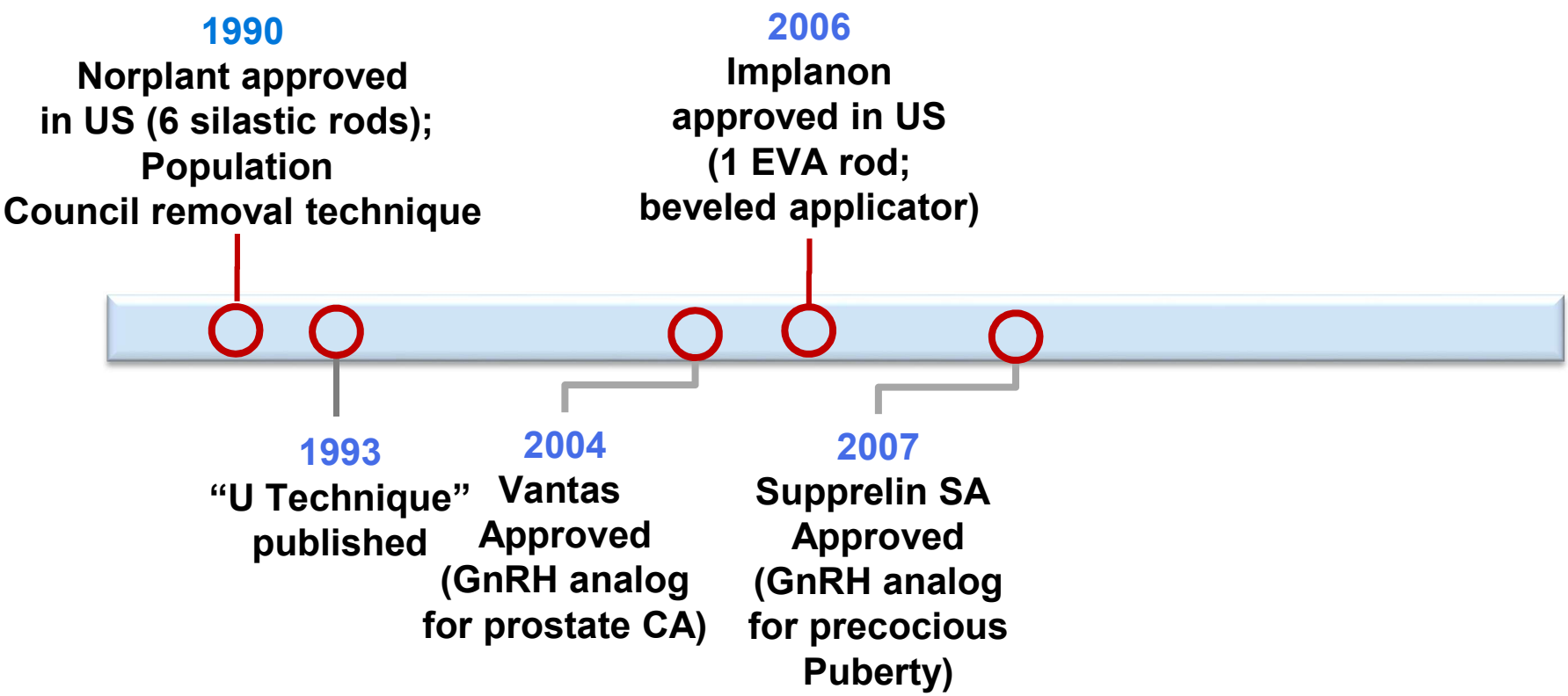
Chronology of Implantable Drug Products Approved in the US and Impact on Probuphine Development

1990

Norplant approved in US (6 silastic rods); Population Council removal technique



Chronology of Implantable Drug Products Approved in the US and Impact on Probuphine Development



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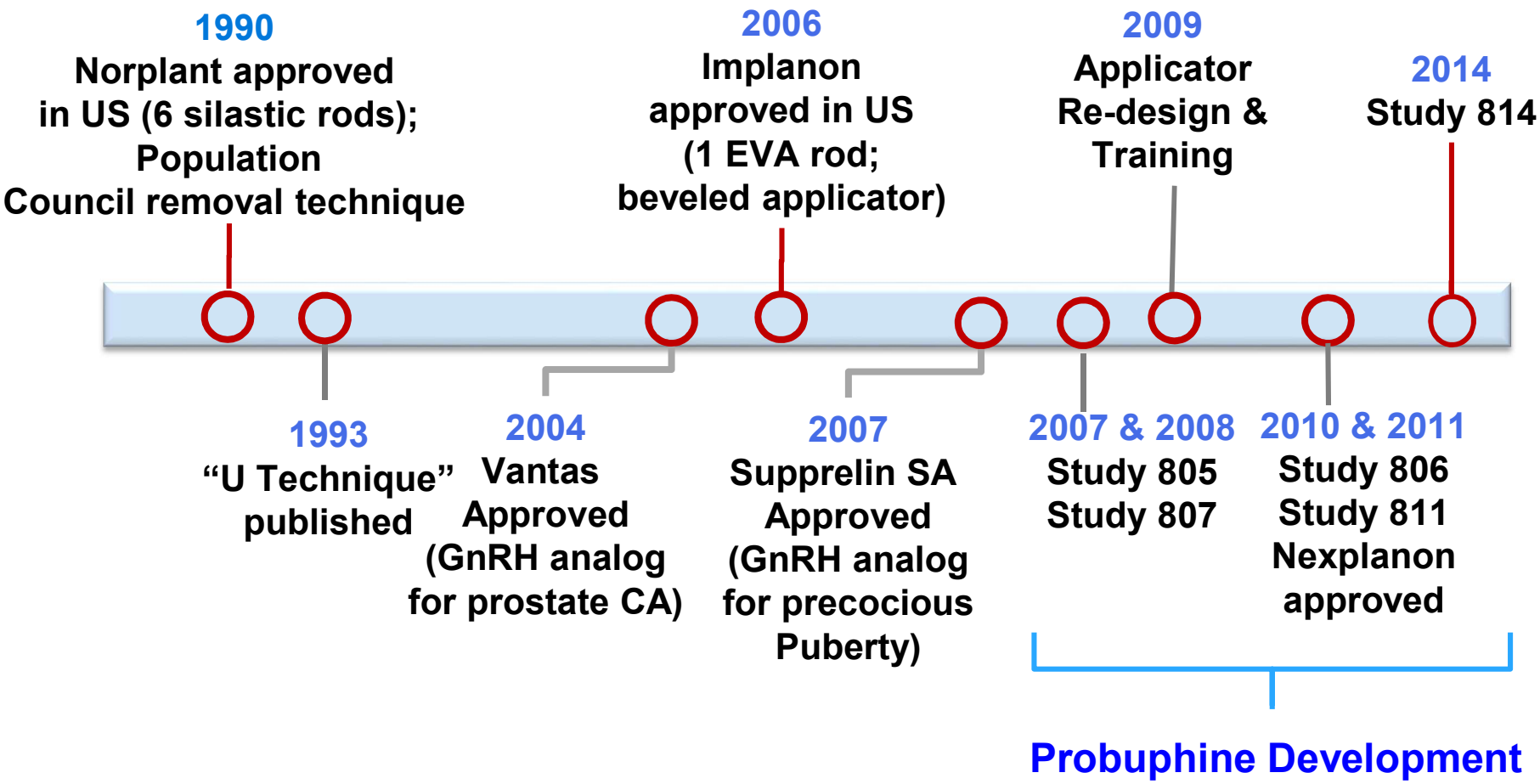


Enhancements:
Equipment and Procedure

	Studies 805 and 807	Studies 806, 811 and 814
Applicator	Blunt	Beveled
Removal technique	Standard technique	"U" technique
Removal clamp	Straight	Modified vasectomy clamp

Original
Blunt-Tipped Applicator

Final
Bevel-Tipped Applicator

Modified Vasectomy Clamp

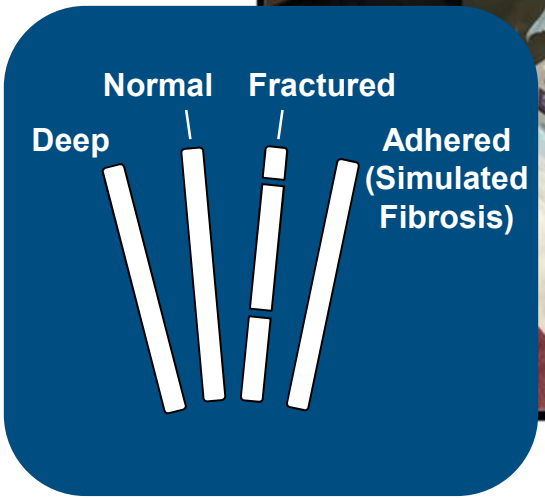
Enhancements:
Competency Based Training

Study 805/807	Study 806/811/814
• Instructional DVD • Self-guided written instructions • On-site training by implant medical monitor if needed	• Training manual • Training video • Half-day training class • Hands-on training using a meat simulation model

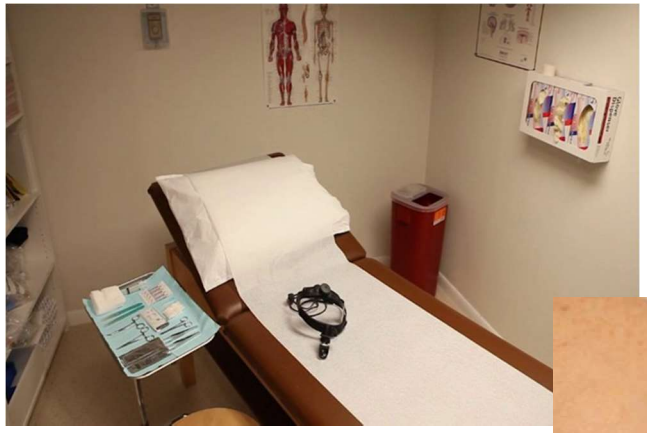
Human Factors Validation:
Competency Based Training

Components of the Validated Training Program

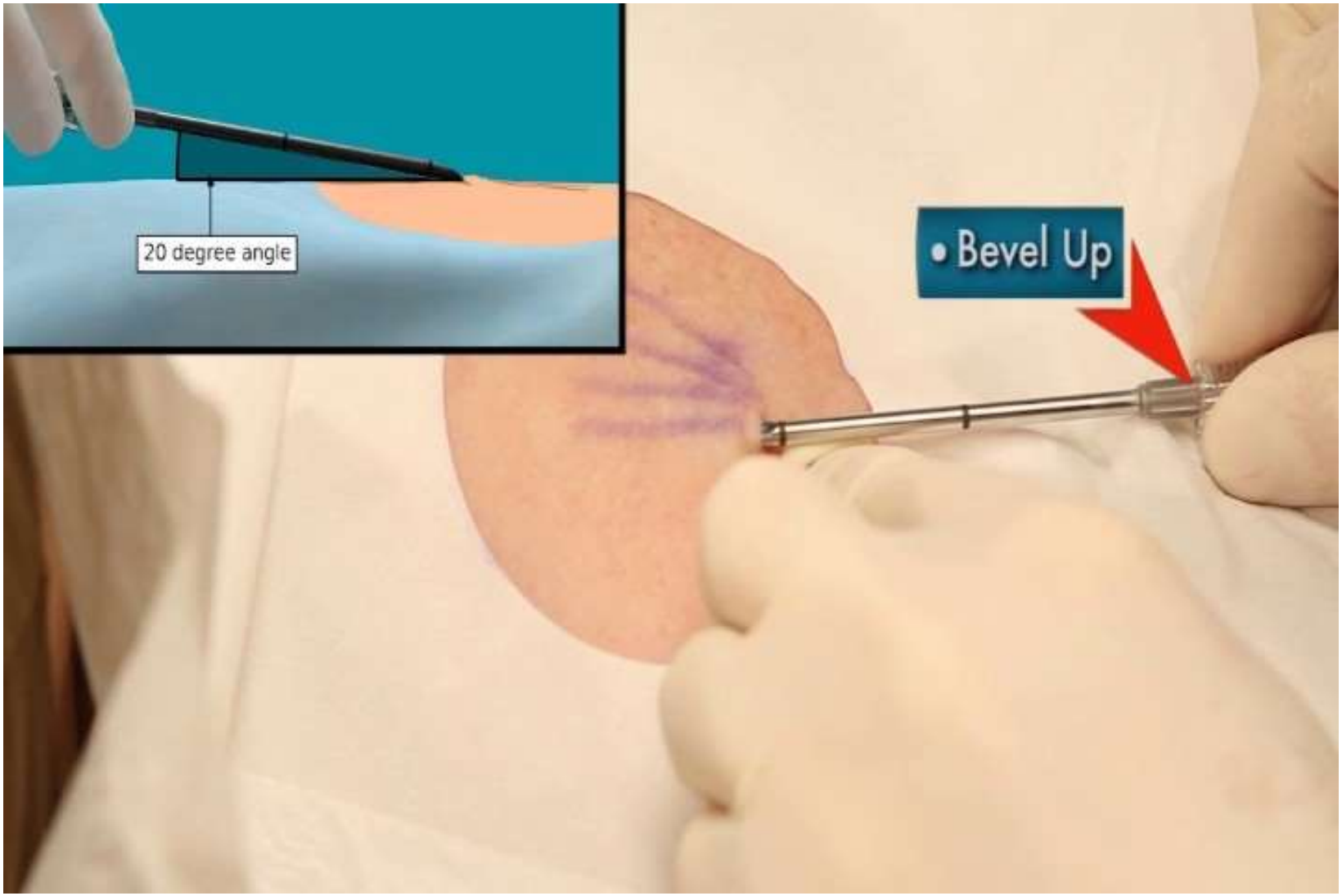
- **Implant Training Procedure**
- **Insertion and Removal Procedure Live Practicum**
- **Certification Exam**



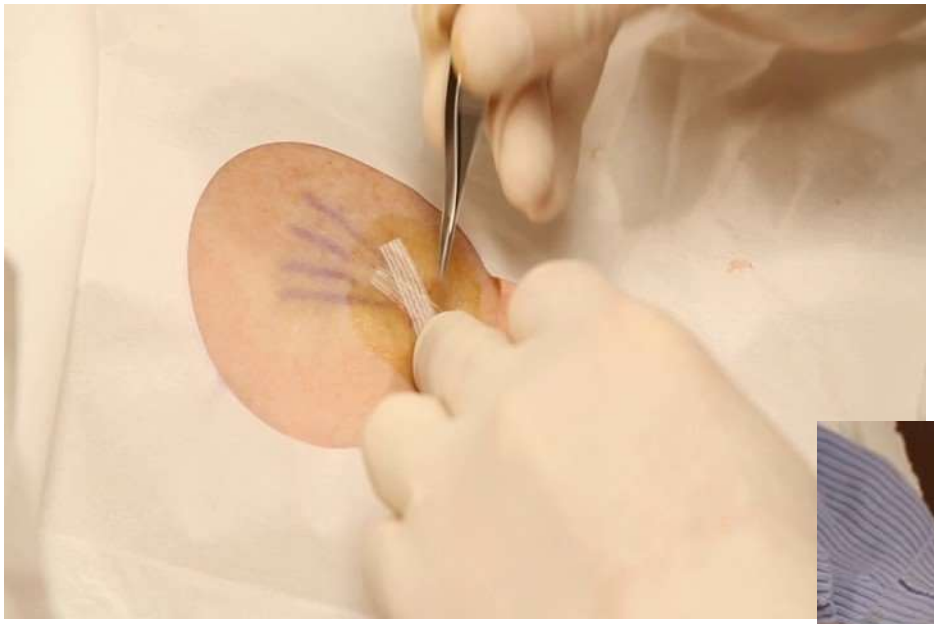
Implant Procedures:
Setup and Patient Preparation



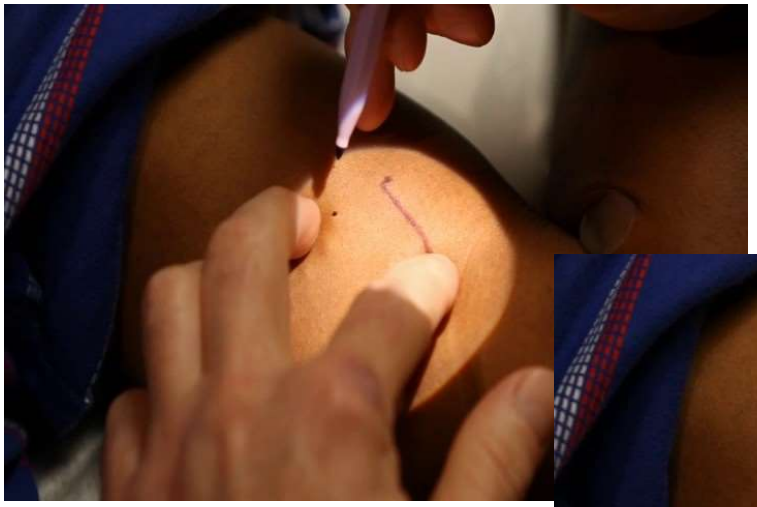
Implant Procedures:
Local Anesthesia, Incision, and Insertion



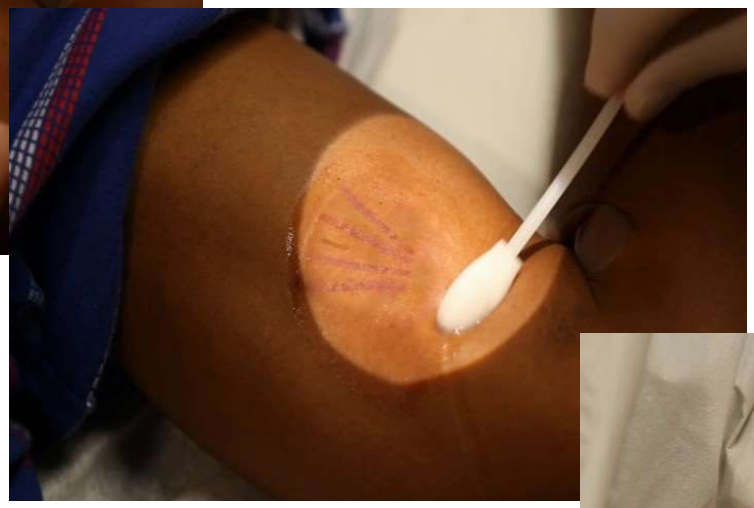
Implant Procedures:
Finishing



Removal Procedures:
Patient Preparation, Local Anesthesia, and Incision



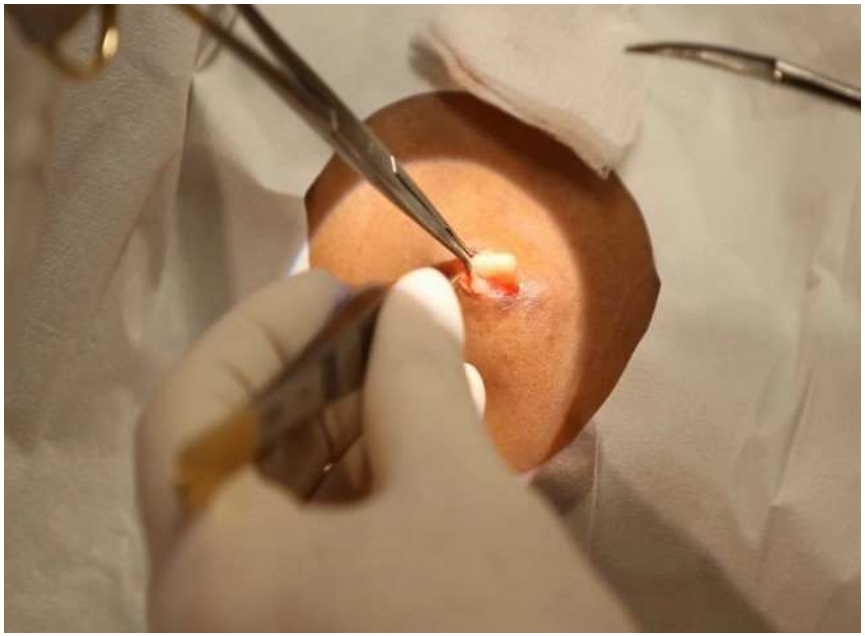
Mark implant locations



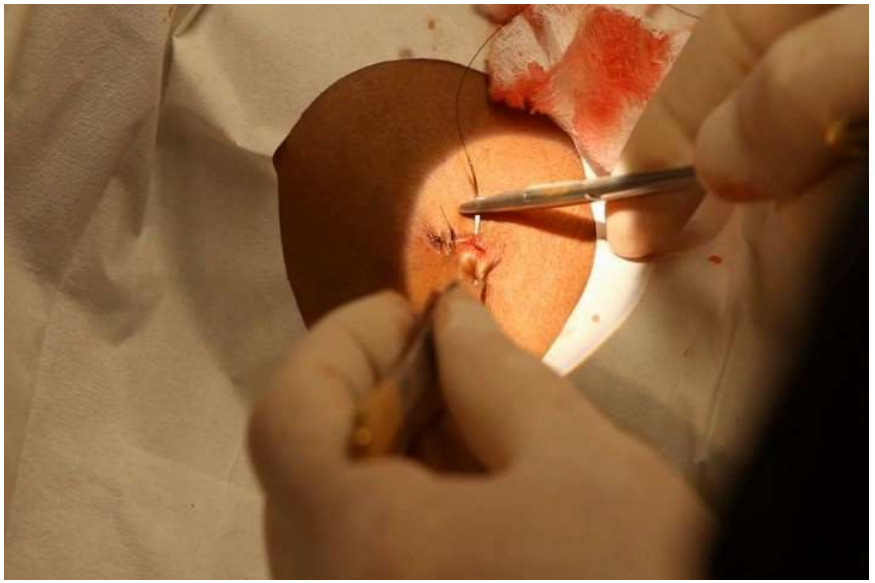
Prep area

Administer local anesthetic

Removal Procedures:
Implant Removal and Finishing



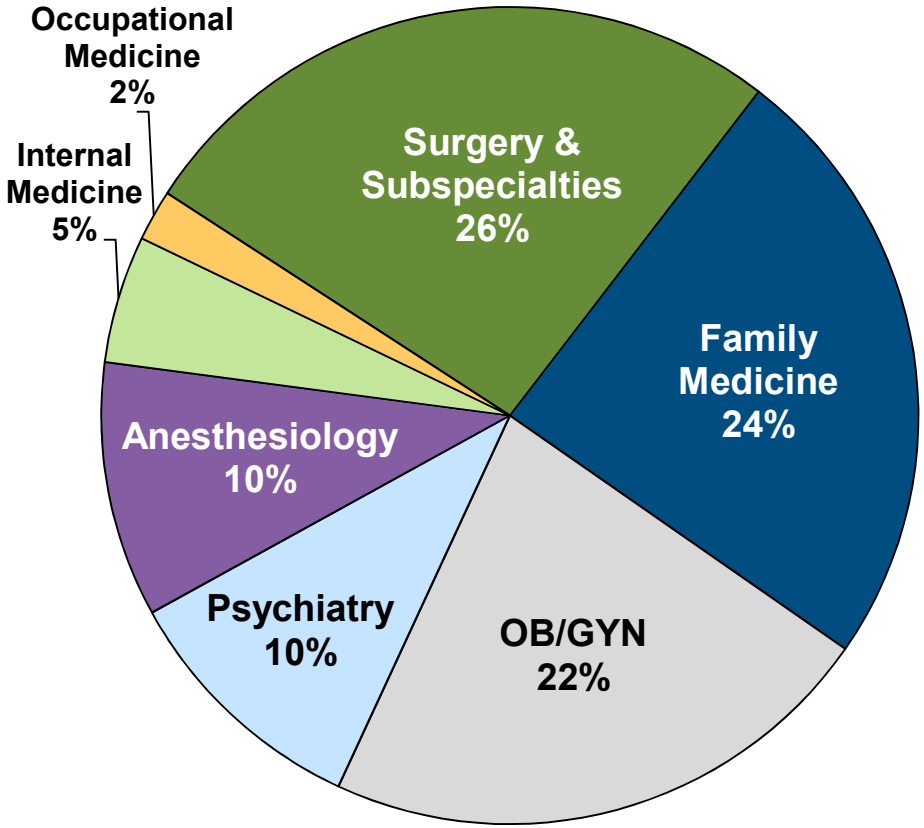
Modified “U” technique



Suture the incision

Medical Specialties of Implanting Physicians

Former Studies



Study 814

- Family Medicine
- Internal Medicine
- Obstetrics & Gynecology
- Neurology and Psychiatry
- General Surgery
- Anesthesiology
- Certified Nurse Practitioner, Family Medicine
- Radiation Medicine, Oncology

Probuphine Safety Review

- **Safety database – 7 clinical studies**
  - Pooled double blind studies (805, 806, and 814)
  - Open-label extension studies (807 and 811)
  - Pharmacology studies (810 and TTP-400)
- **Buprenorphine drug substance**
  - Well-characterized
- **Probuphine implant and related procedures**
  - Safety review focuses on unique delivery system and procedures

Probuphine Exposure in Controlled and Open Label Studies

	N
Total patients exposed	**370**
≥6 months	151
≥12 months	85

Long term exposure: One recent case where a subject returned to the study site approximately 7 years after insertion

Implant Exposures

	N
Placebo implants	198
Probuphine implants	370
Total implants	568

Safety During Double-blind Clinical Trials

	Study 805		Study 806			Study 814	
	Probuphine N=108 %	Placebo N=55 %	Probuphine N=114 %	Placebo N=54 %	SL BPN N=119 %	Probuphine N=87 %	Placebo/ SL BPN N=89 %
Any adverse event	**86.1**	**81.8**	**71.9**	**66.7**	**71.4**	**57.5**	**56.2**
Leading to discontinuation	3.7	0	1.8	3.7	4.2	1.1	0
SAE	1.9	7.3	5.3	5.6	5.9	2.3	3.4
Death	0	0	0	0	0.8	0	0

Safety During Double-blind Clinical Trials

	Study 805		Study 806			Study 814	
	Probuphine N=108 %	Placebo N=55 %	Probuphine N=114 %	Placebo N=54 %	SL BPN N=119 %	Probuphine N=87 %	Placebo/ SL BPN N=89 %
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Leading to discontinuation	3.7	0	1.8	3.7	4.2	1.1	0
SAE	1.9	7.3	5.3	5.6	5.9	2.3	3.4
Death	0	0	0	0	0.8	0	0

One Death
PRO-806 -- SL Buprenorphine Group

- **29 year old woman**
- **Heroin overdose 3 days after she withdrew**
- **Randomized to SL BPN treatment group**
- **In treatment for ~3 months**
- **Last SL BPN**
  - Fourteen 8 mg tablets 10 days before death

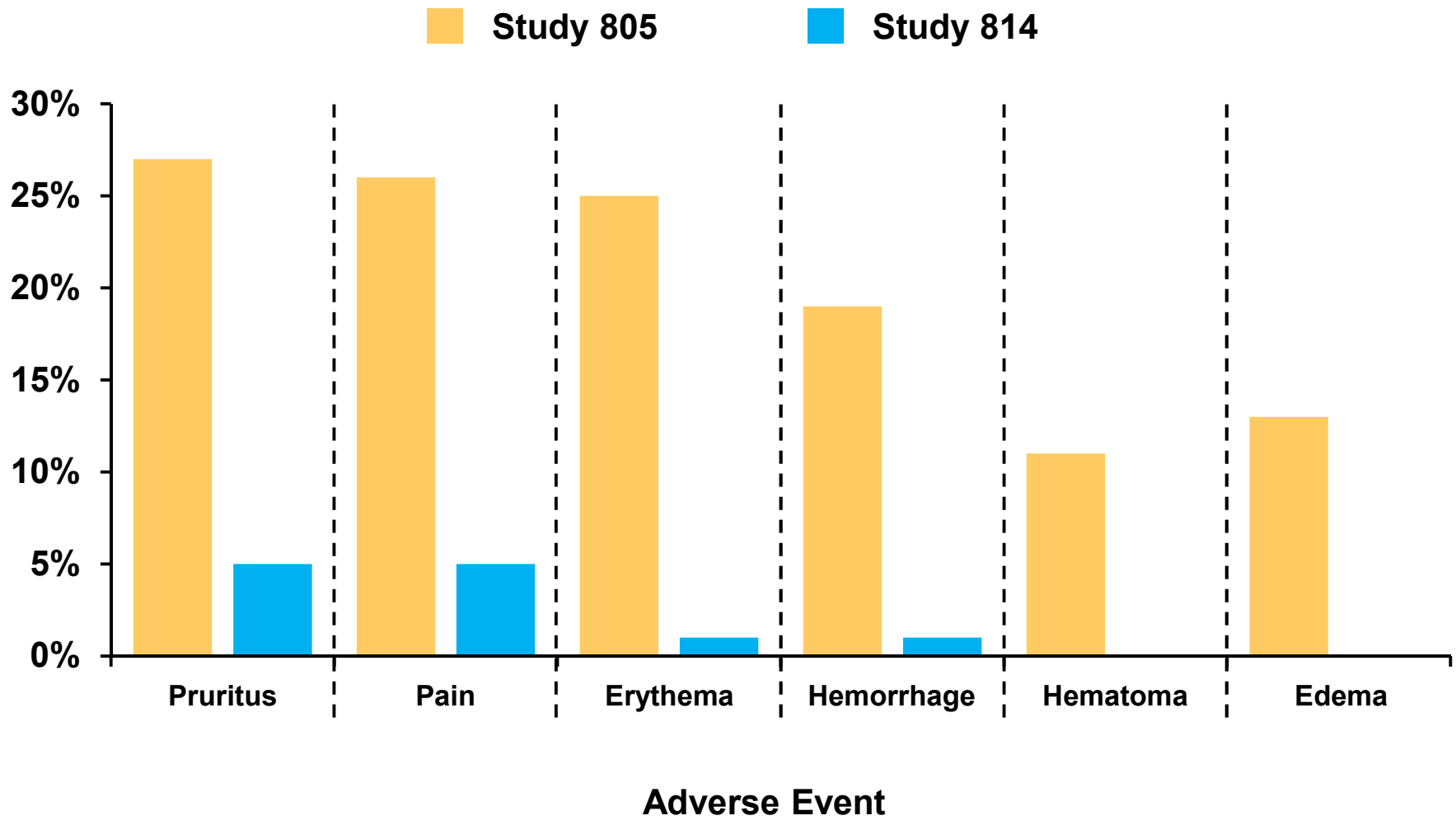
Events of Interest in PRO-814

- **Pediatric exposure**
  - Hospitalization of study subject's 2 year old child accidentally exposed to SL BPN
- **Entered drug rehabilitation facility**
  - Two subjects in the SL BPN group entered rehab facilities
- **Theft**
  - Two cases alleged theft of active SL BPN and placebo tablets

Most Common Non-implant Site AE (Events >5%)
Pooled Double-blind Studies

	Probuphine N=309 %	Placebo/SL BPN N=317 %
Any non-implant site AE	**64.7**	**64.7**
Headache	12.6	10.1
Insomnia	8.4	11.4
Nasopharyngitis	8.7	6.9
Upper respiratory tract infection	8.1	7.3
Nausea	6.5	4.7
Anxiety	4.9	5.7
Back pain	5.8	4.7
Depression	6.5	3.2
Constipation	6.5	2.8
Vomiting	5.5	3.5

Common Implant Site Related Adverse Events From PRO-805 to PRO-814



Implant Site Infections

	Study 805		Study 806		Study 814	
	Probuphine n (%)	Placebo n (%)	Probuphine n (%)	Placebo n (%)	Probuphine n (%)	Placebo/ SL BPN n (%)
Any implant site Infection	**4 (3.7)**	**1 (1.8)**	**1 (0.9)**	**2 (3.7)**	**3 (3.4)**	**3 (3.4)**
Implant site infection	4 (3.7)	1 (1.8)	1 (0.9)	2 (3.7)	0	1 (1.1)
Cellulitis	0	1 (1.8)	0	0	1 (1.1)	1 (1.1)
Post-operative wound infection	0	0	0	1 (1.9)	1 (1.1)	1 (1.1)
Purulent drainage from explant site	0	0	0	0	1 (1.1)	0

Discontinuations Due to Implant Site AEs

- **Total of 6 subjects across all studies**
  - No implant site adverse events led to study discontinuations in Studies 806, 811, and 814

Study	Subject	Adverse Event	Relation to Procedure	Outcome	
PRO-805	1	Hepatic enzyme increased	Not related	Recovering/Resolving	Probuphine
	2	Implant site pain	Possibly related	Recovered/Resolved	Probuphine
		Implant site infection	Possibly related	Recovered/Resolved	Probuphine
	3	Implant site infection	Possibly related	Recovered/Resolved	Probuphine
		Implant site pain	Possibly related	Recovered/Resolved	Probuphine
	4	Implant site pain	Possibly related	Recovered/Resolved	Probuphine
PRO-807	5	Implant site hemorrhage	Not related	Recovering/Resolved	Probuphine
		Implant site infection	Not related	Recovering/Resolved	Probuphine
		Implant site edema	Not related	Recovering/Resolved	Probuphine
		Implant site erythema	Not related	Recovering/Resolved	Probuphine
	6	Implant site infection	Not related	Recovering/Resolved	Probuphine

Safety Conclusions

- **BPN: Well-characterized safety profile**
- **Probuphine safety comparable to approved BPN**
- **Mild to moderate implant-related adverse events**
  - Rates decreased with improvements in equipment, procedures, and training

Risk Management

Behshad Sheldon

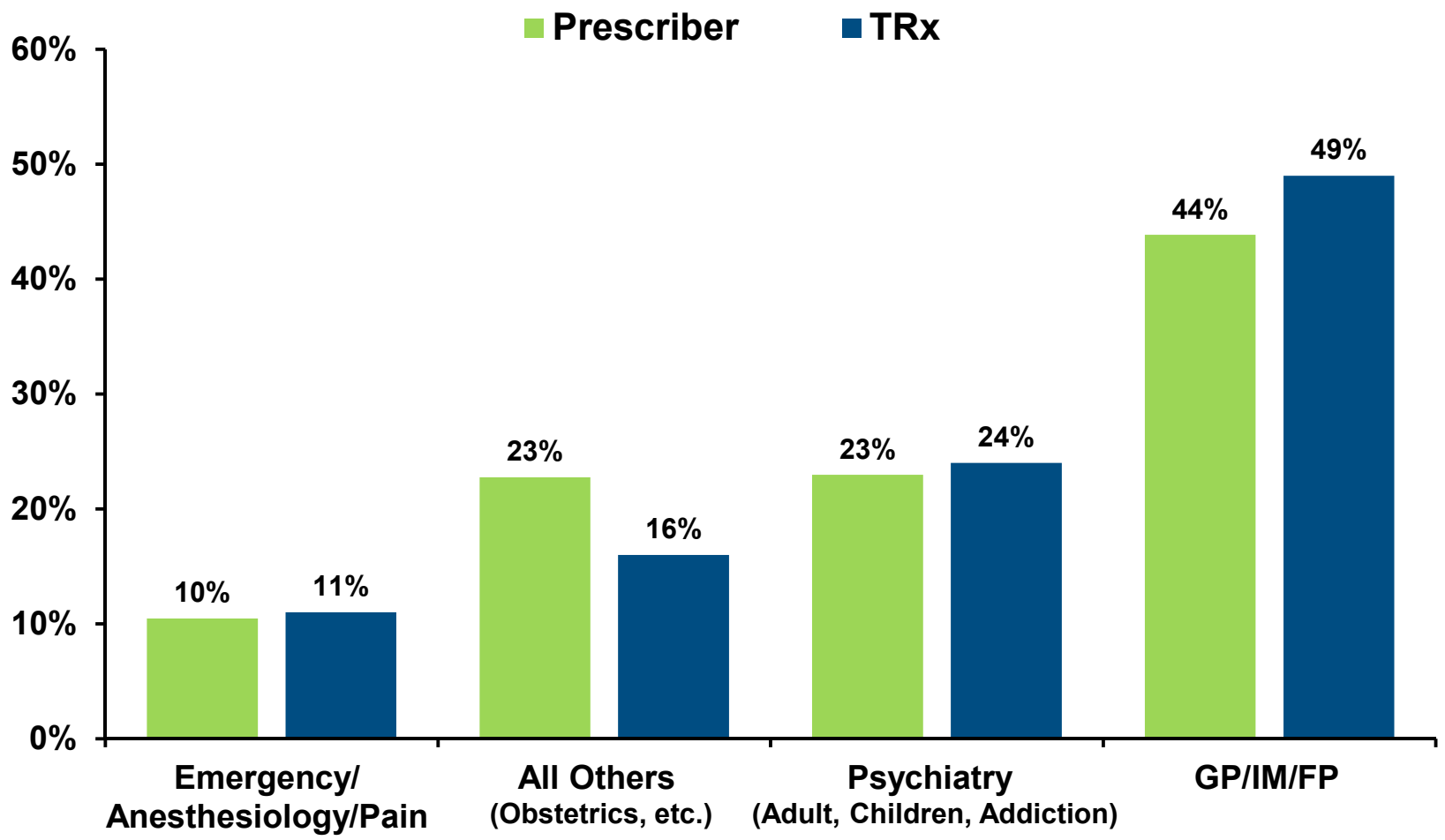
President and CEO
Braeburn Pharmaceuticals

Probuphine REMS Goal

- **To mitigate (1) the risk of complications of migration, protrusion, expulsion and nerve damage associated with the improper insertion and removal of Probuphine and (2) the risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin by:**
  - Educating providers
  - Informing patients about the risks of complications
  - Distributing Probuphine only to trained and certified healthcare providers

Training of Healthcare Providers

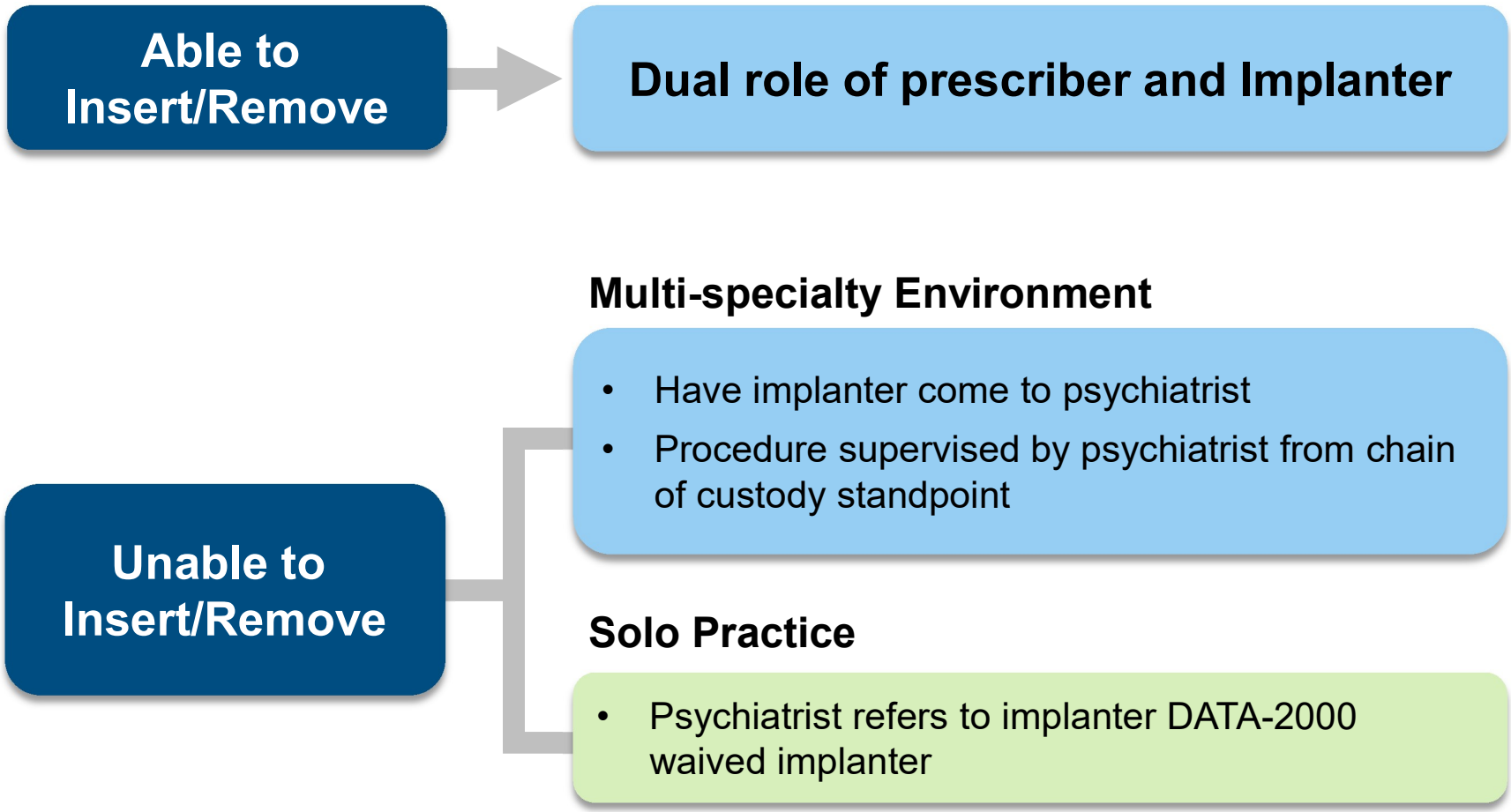
Buprenorphine Prescribers and TRx Comparison by Specialty



Source: TRx data from Symphony Health Solutions, period May 2014-April 2015

CR-91

Model of Care for Psychiatrists



Certification Requirements by Clinician Type

Requirement	HCP who Prescribes	HCP who Inserts/Removes
Didactic training and live practicum	✓	✓
Knowledge Assessment Test	✓	✓
Counseling patients (Patient Counseling Tool / Med Guide)	✓	✓
Maintain Insertion/Removal Log (in medical record)	✓	✓
Supervise certified HCP in insertion/removal	✓	
Live Practicum Procedural Competency Assessment Test		✓
Ensure appropriate equipment at facility		✓

Certification Requirements by Clinician Type

Requirement	HCP who Prescribes	HCP who Inserts/Removes
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Supervise certified HCP in insertion/removal	✓	
Live Practicum Procedural Competency Assessment Test		✓
Ensure appropriate equipment at facility		✓

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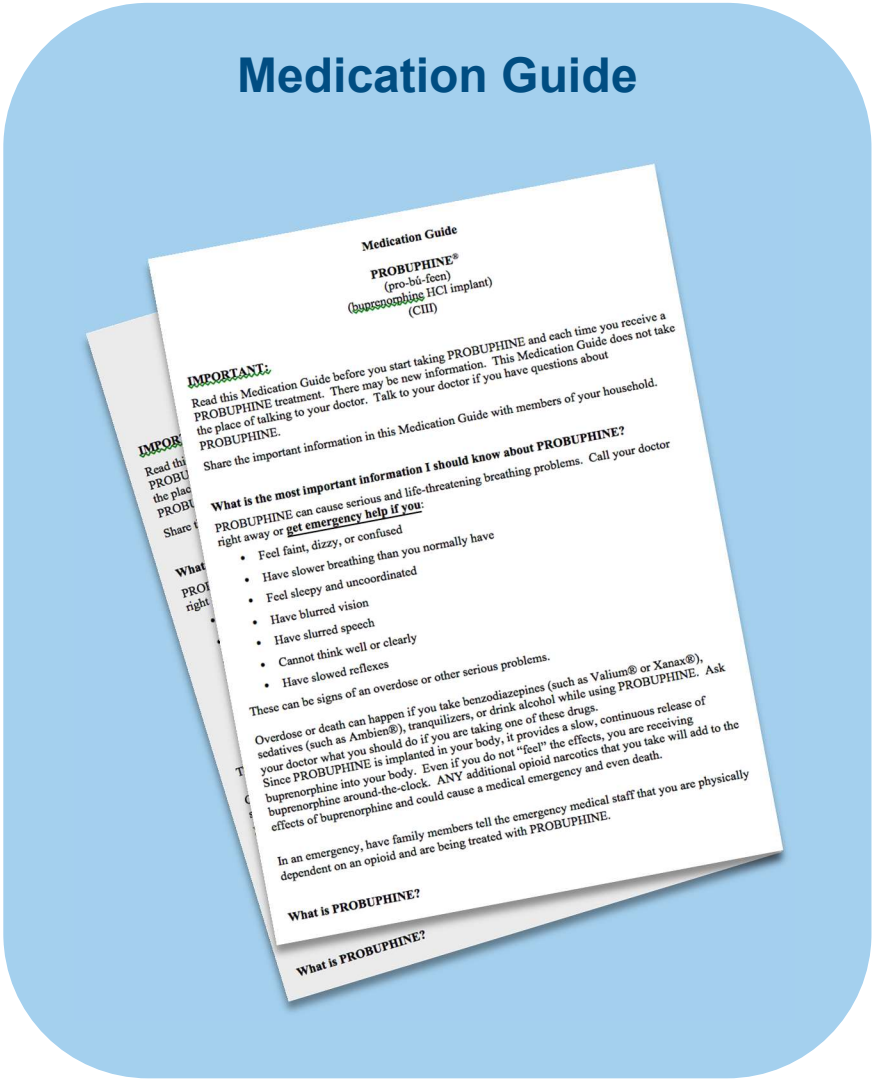
Maintain Insertion/Removal Log (in medical record)	✓	✓
Supervise certified HCP in insertion/removal	✓	
Live Practicum Procedural Competency Assessment Test		✓
Ensure appropriate equipment at facility		✓

Healthcare Provider Take-Home Materials

- Insertion and removal checklist
- Instructions for use booklet
- Training slides
- Package Insert
- Medication Guide
- Patient counseling tool
- Insertion and removal log

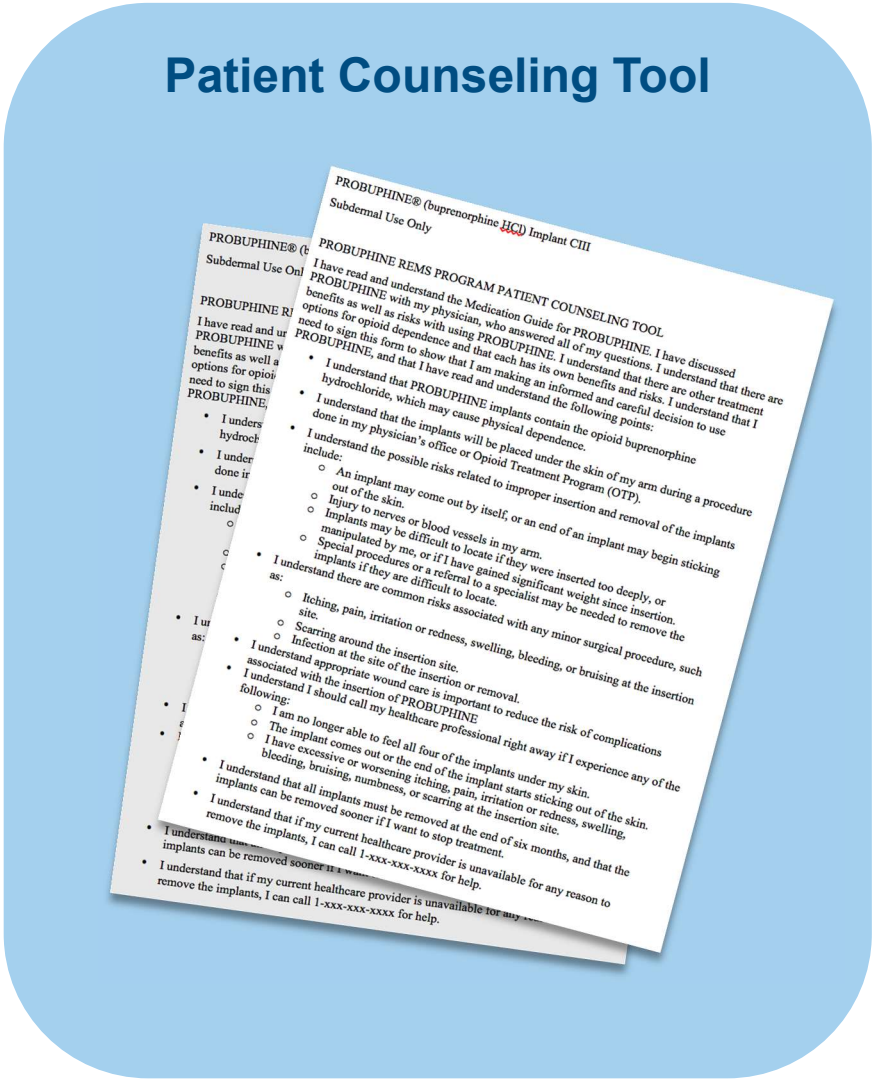
Medication Guide



- Inform about risks associated with Probuphine's insertion and removal procedure
- Instruct how to avoid risks of accidental overdose, misuse, or abuse if an implant comes out or protrudes from the skin

Patient Counseling Tool

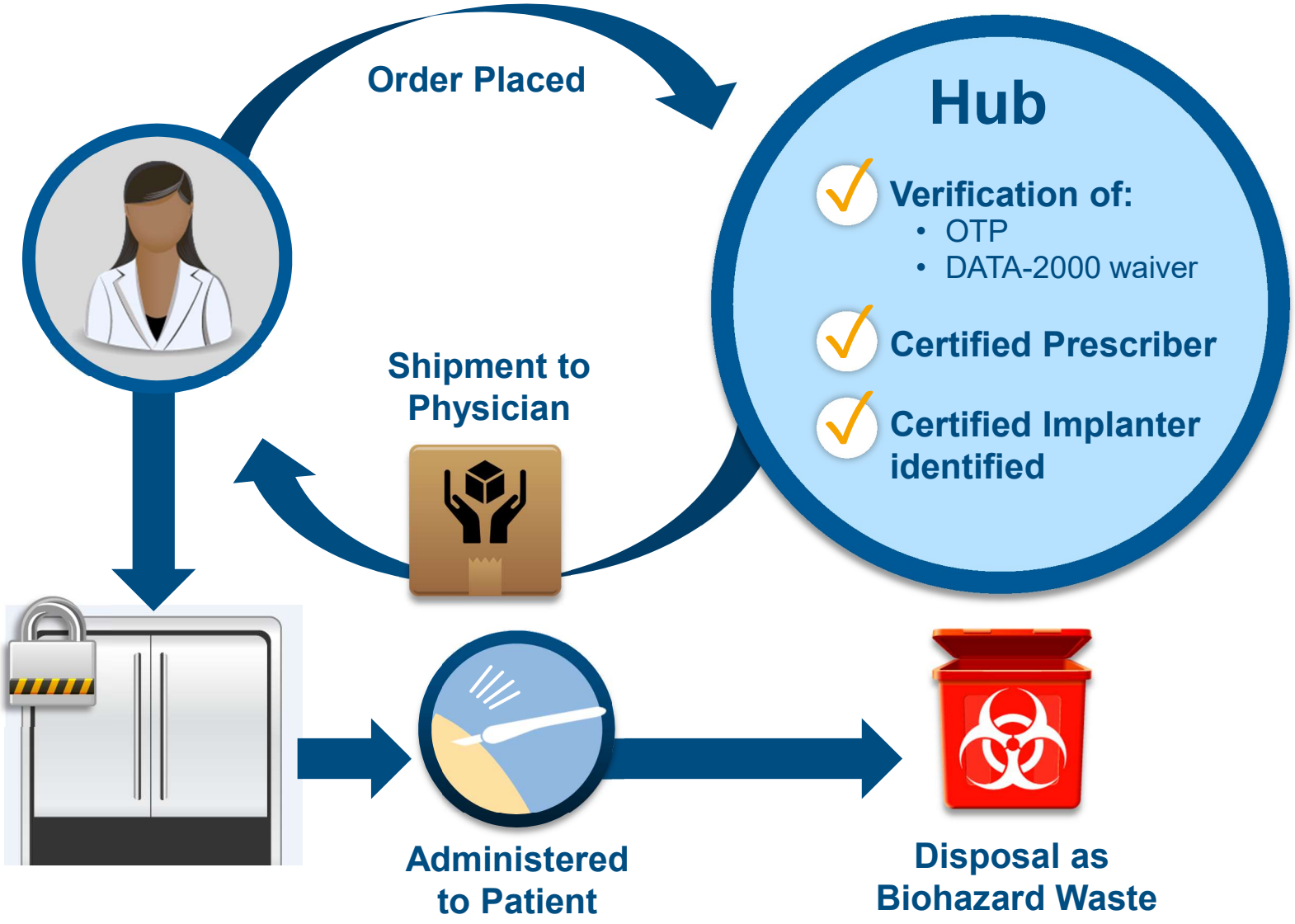
- Healthcare providers will agree to utilize the **Patient Counseling Tool** to confirm awareness of all potential risks. This tool could be signed by the patient and the prescriber.



Probuphine REMS Website

- **Overview of the REMS program**
- **Tools for healthcare providers**
  - Healthcare provider certification requirements
  - Didactic training slides
  - Criteria for procedural competency
  - Insertion/Removal Log
- **Prescribing Information**
- **Medication Guide**
- **Patient Counseling Tool**
- **Information for patients**
- **Adverse event reporting information**
- **Locator for healthcare providers who insert/remove**

Probuphine Closed Distribution System



CR-100

Probuphine REMS Assessment

- **Report on certified prescribers and implanters**
- **Review training, make quality improvements**
- **Monitor and evaluate the closed distribution system**
  - Track orders
  - Review rejected orders, identifying reason for rejection
  - Investigate suspicious orders
  - Investigate any improper shipments by semi-annual audits
- **Investigate irregularities and third-party reports suggesting diversion**
  - Collaborate with licensing boards and law enforcement

Non-REMS Resources

- Insertion and removal toolkits available upon request
- Probuphine clinical educators present at first insertion and removal procedure upon request
- Probuphine master trainers available for consultation
- Additional training programs

Risk Management Program Conclusions

- **Comprehensive system to assure the safe use of Probuphine**
  - Patient and Provider Education
  - Mandatory training and certification for healthcare providers who prescribe and insert/remove
  - Closed distribution system
- **Continuous monitoring**
- **Continuous improvement**

Conclusion and Benefit/Risk Assessment

Michael P. Frost MD, FACP, FASAM

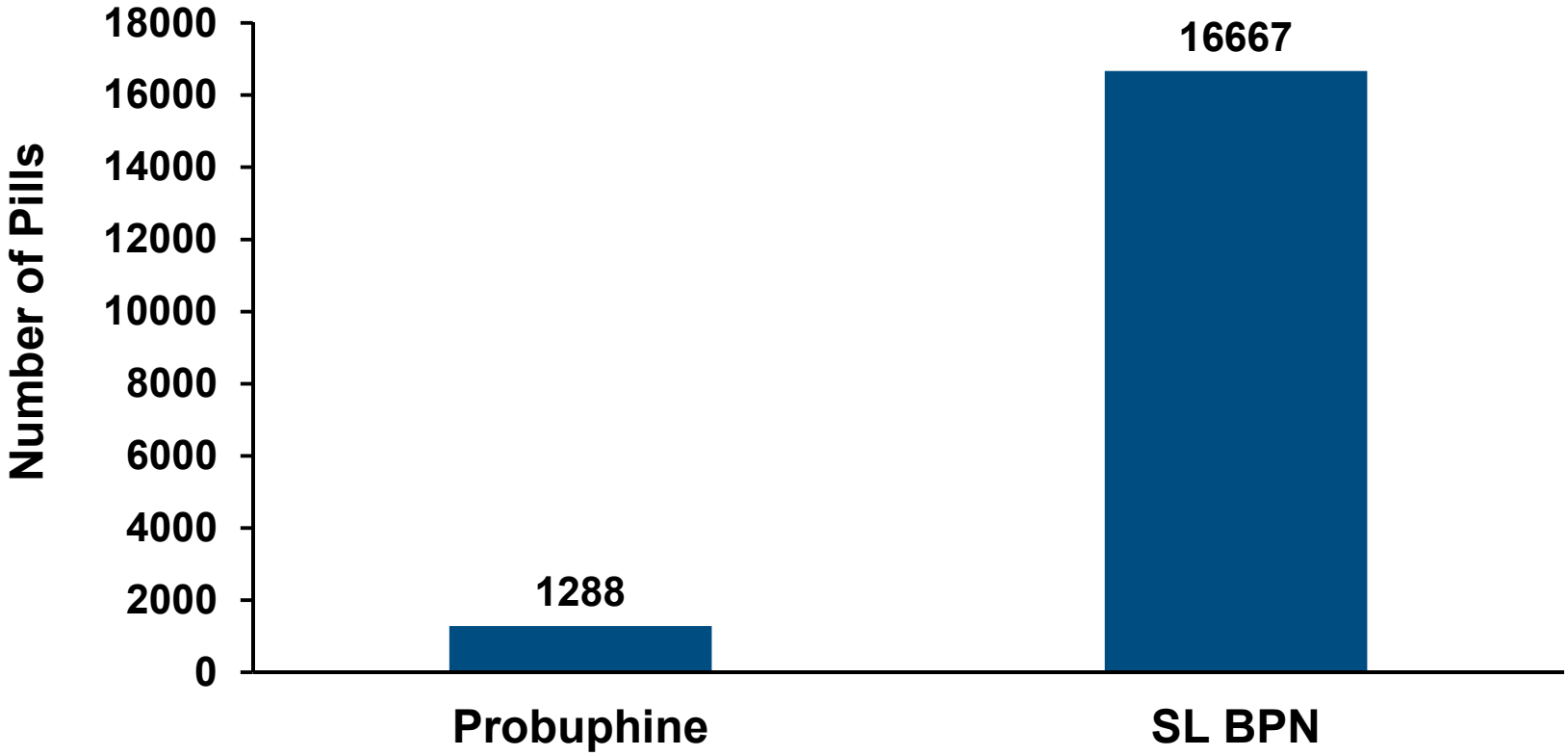
Medical Director
Eagleville Hospital

President
Frost Medical Group

Benefits

- **Effective for clinically stable patients**
  - 96.4% of Probuphine subjects met the responder definition compared with 87.6% of SL BPN subjects
  - 85.7% of Probuphine subjects had no evidence of illicit opioid use throughout the trial compared with 71.9% SL BPN subjects
- **Reduced risk of diversion, abuse, misuse and accidental exposure**

Total Pill Exposure – Study 814



CB-106

Meeting the Needs of Stable Patients

- Eliminate anxiety about medication availability
- Reduce accidental exposure
- Improve convenience
- Reduce stigma
- Restore “normality”

Risks

- **Drug substance**
  - Well characterized
  - Probuphine experience consistent with transmucosal buprenorphine products
- **Insertion and removal procedure**
  - Pooled clinical studies showed
    - No deaths or SAEs requiring hospitalization related to Probuphine
    - Mild, localized, transient bleeding, pain, swelling, or infection
  - Training program effective for clinical trials
- **Supplemental use**

Benefit-Risk Conclusion

- **Benefits**
  - Effective in clinically stable patients
  - Assurance of continuous medication delivery
  - Reduced stigma and enhanced privacy
  - Patient convenience
- **Public health benefits**
  - Additional treatment option
  - Reduced risk of diversion, misuse, abuse and accidental pediatric exposure
- **Risks**
  - Shared with other buprenorphine medications while the risks related to the implantation and removal are moderate and transient

Sponsor Experts Available

Andrea Barthwell, MD, FASAM
Medical Director
Encounter Medical Group, P.C.

Michael Chen, PhD
President
TCM Groups

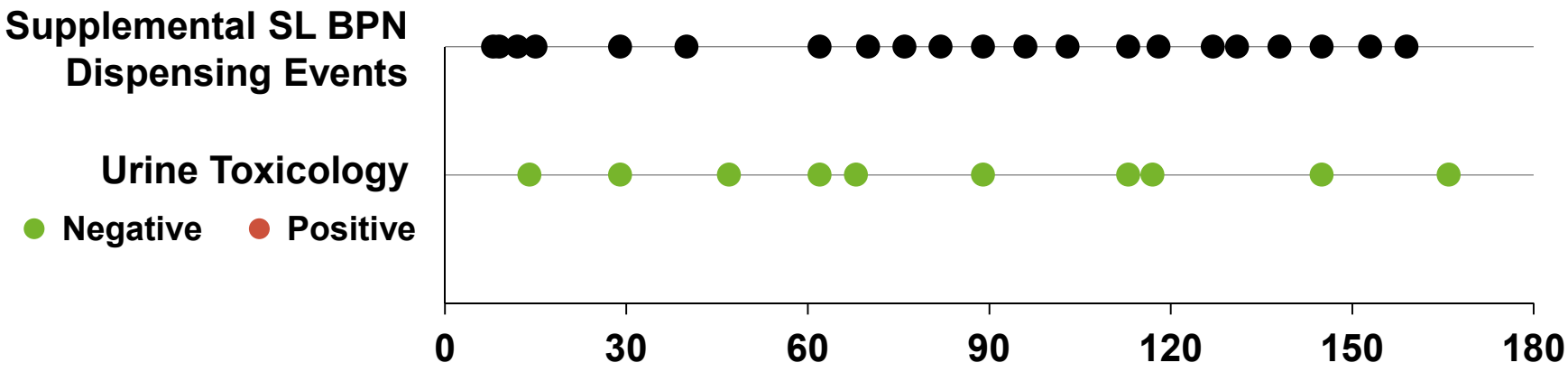
Matthew Torrington, MD
Family and Addiction Medicine Physician
Medical Director, Common Ground/End Dependence Free Clinic

Frank Vocci, PhD
President/ Senior Research Scientist
Friends Research Institute

Sharon Walsh, PhD
Professor of Behavioral Science, Psychiatry, and Pharmaceutical Sciences
Director of the Center on Drug and Alcohol Research
University of Kentucky

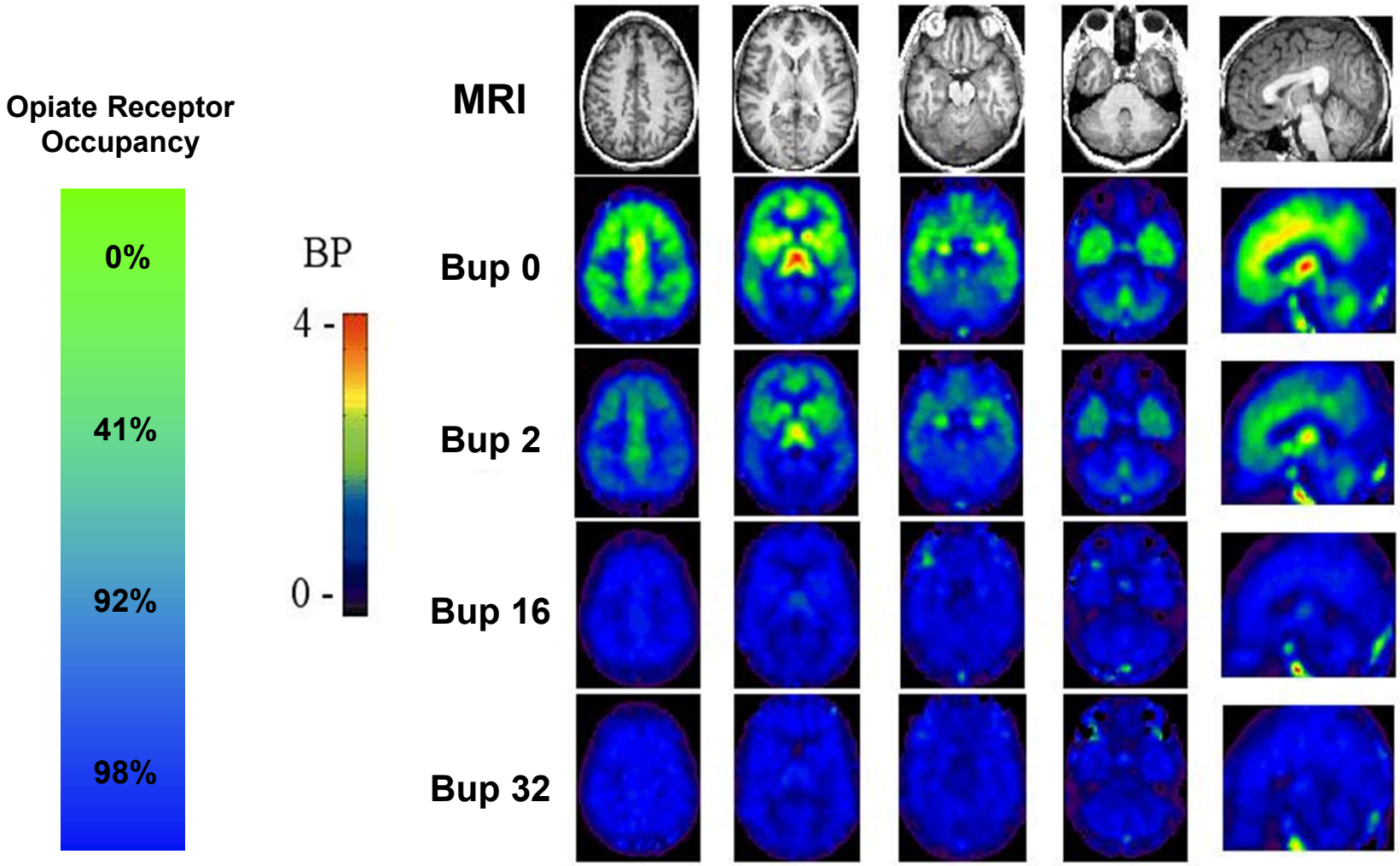
Lee-Jen Wei, PhD
Professor of Biostatistics
Harvard University

Subject 019-008 (Probuphine): Clinical Outcomes



Reason for Use:
"Situational Anxiety/Depression"

Buprenorphine Opiate Receptor Occupancy



M.K. Greenwald et al. *Neuropsychopharmacology*. 2003.

Greenwald, Comer & Fiellin, 2014

Withdrawal Suppression

~BUP 4 mg

(≤50% OR availability)

Opioid Blockade

>BUP 16 mg

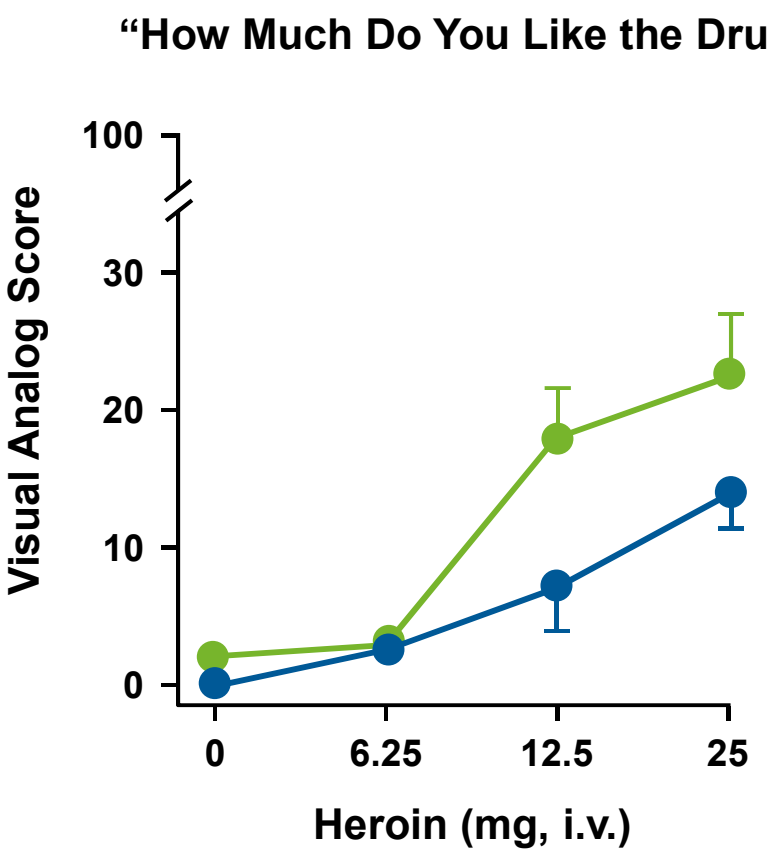
(<20% OR availability)

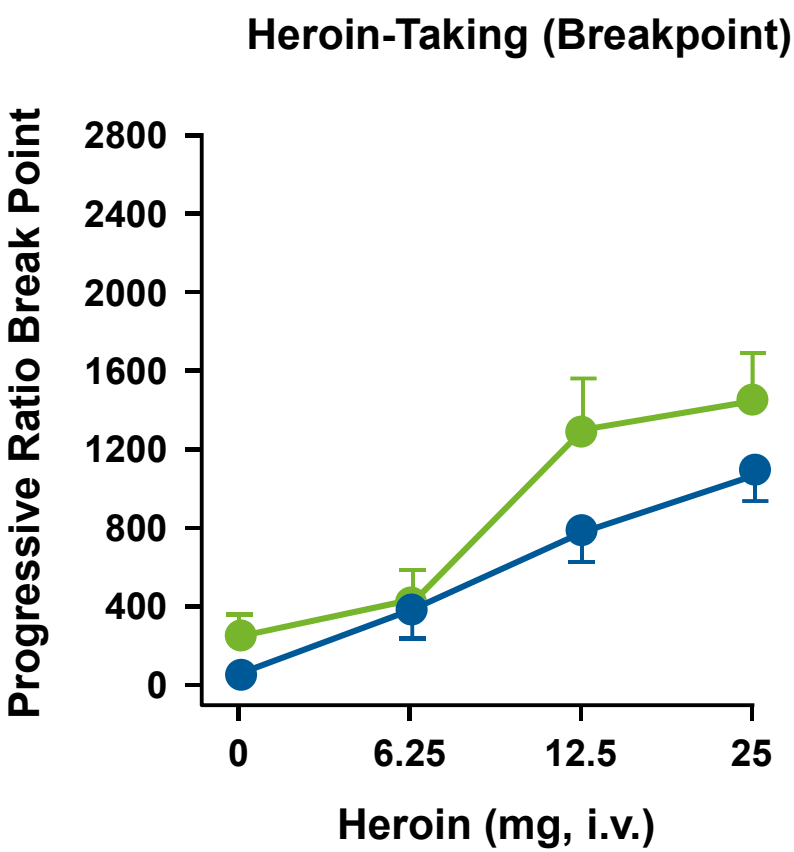
Responder Rates by Current Dose
ITT Population

Category	Probuphine n (%)	SL BPN n (%)
Patients who Received 8 mg		
N	59	67
Responder	58 (98)	57 (85)
Non-responder	1 (2)	10 (15)
Patients who Received <8 mg		
N	25	22
Responder	23 (92)	21 (95)
Non-responder	2 (8)	1 (5)
Overall responder rate	**96%**	**88%**

Buprenorphine: Heroin Self-Administration

Buprenorphine: 8 mg 16 mg



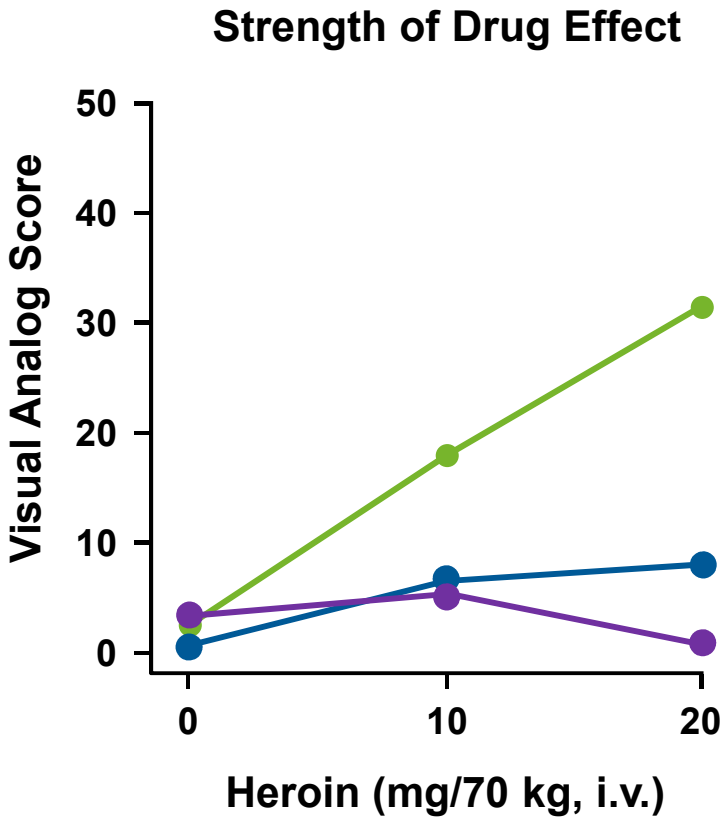


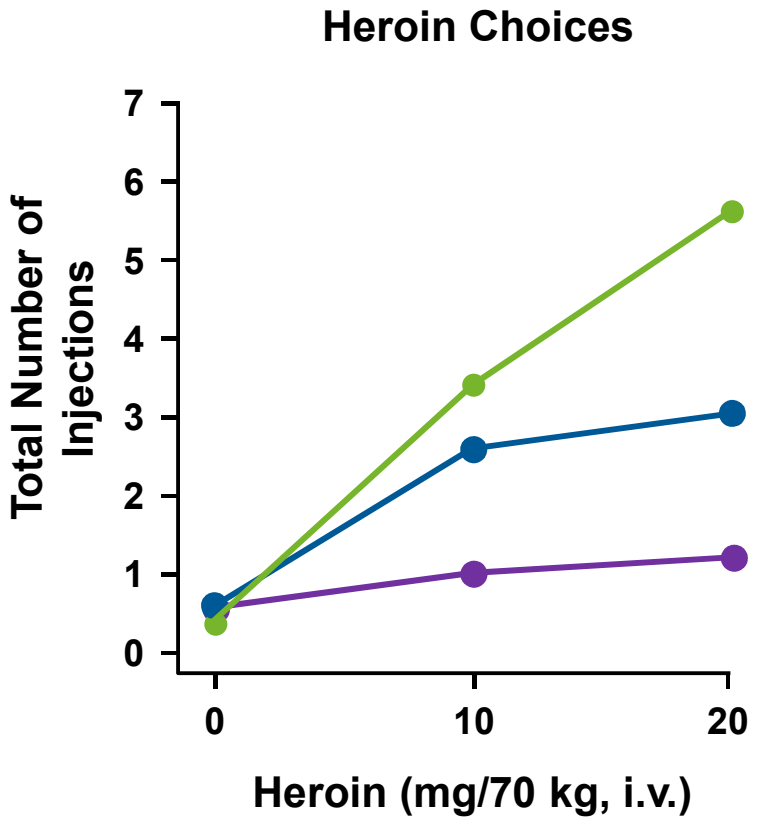
Comer, Collins and Fischman. *Psychopharmacology.* 2001; 154: 28-37.

CP-4

Methadone and Heroin:
Subjective Effects and Self-administration

Methadone (mg/day): 50 100 150





Donny, Brasser, Bigelow, Stitzer & Walsh. *Addiction*. 2005; 100: 1496-1509

CP-5

Opioid Use History by Route of Administration

Heroin

TRTP (Planned Treatment)	IV	Inhalation
SL BPN	15/22	7/22
Probuphine	12/15	3/15

Rx

TRTP (Planned Treatment)	IV	Inhalation
SL BPN	6/66	8/66
Probuphine	7/65	12/65

Urine Toxicology Results at Screening
PRO-814

Visit	Result	Probuphine N=84 n (%)	SL BPN N=89 n (%)	Total N=173 n (%)
Amphetamine	Negative	78 (92.9)	82 (92.1)	160 (92.5)
	Positive	6 (7.1)	7 (7.9)	13 (7.5)
Barbiturates	Negative	83 (98.8)	89 (100.0)	172 (99.4)
	Positive	1 (1.2)	0 (0.0)	1 (0.6)
Benzodiazepine	Negative	76 (90.5)	81 (91.0)	157 (90.8)
	Positive	8 (9.5)	8 (9.0)	16 (9.2)
Benzoylecgonine	Negative	84 (100.0)	88 (98.9)	172 (99.4)
	Positive	0 (0.0)	1 (1.1)	1 (0.6)
Cannabinoids	Negative	70 (83.3)	75 (84.3)	145 (83.8)
	Positive	14 (16.7)	14 (15.7)	28 (16.2)
Phencyclidine	Negative	82 (97.6)	89 (100.0)	171 (98.8)
	Positive	2 (2.4)	0 (0.0)	2 (1.2)

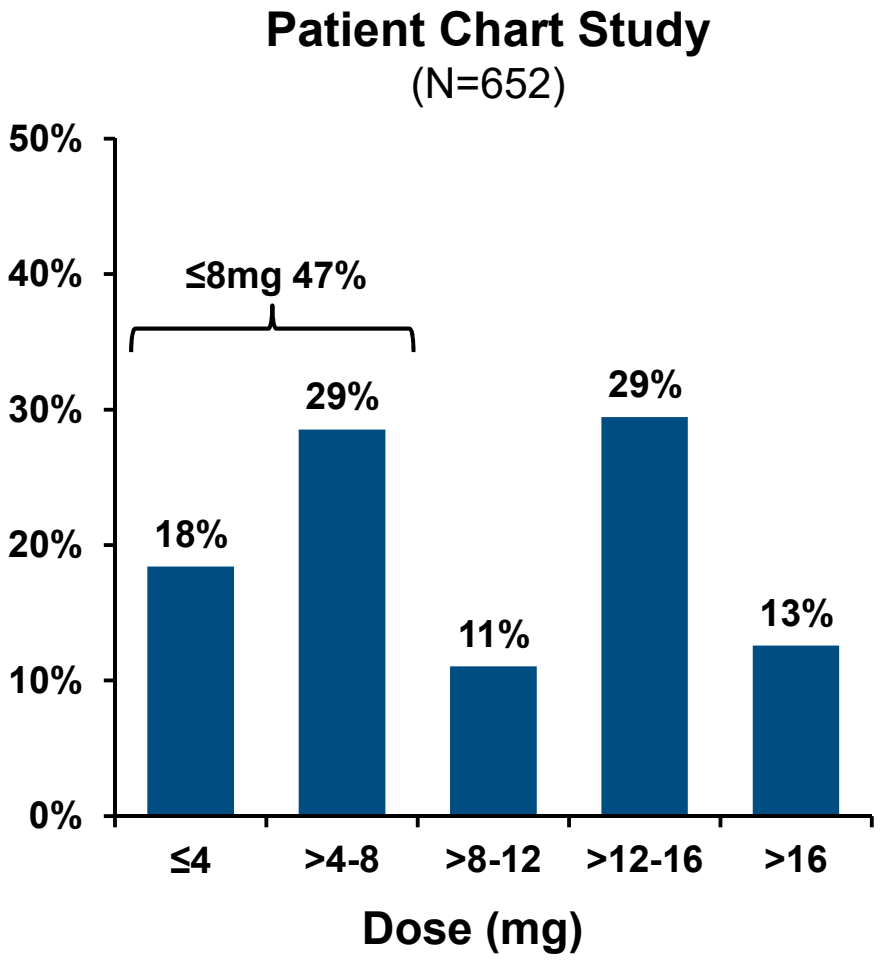
Urine Toxicology Results: Amphetamine
Study PRO-814

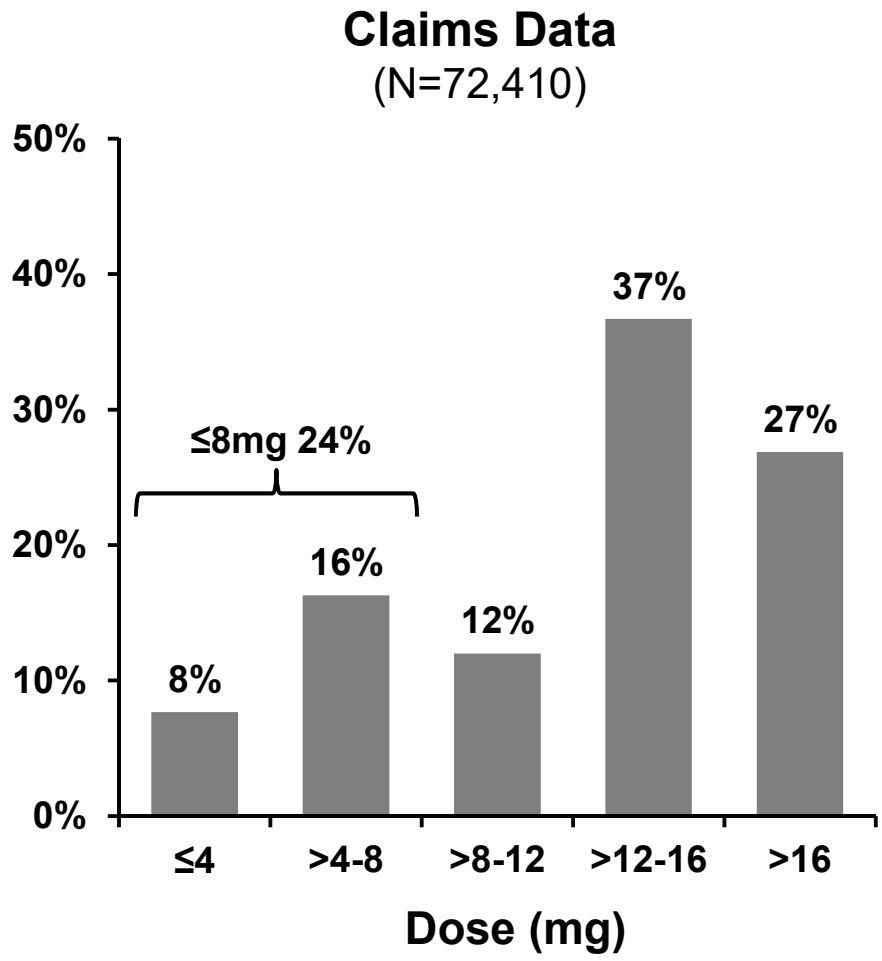
Visit	Result	Probuphine N=84 n (%)	SL BPN N=89 n (%)	Total N=173 n (%)
Screening	Negative	78 (92.9)	82 (92.1)	160 (92.5)
	Positive	6 (7.1)	7 (7.9)	13 (7.5)
Week 4	Negative	77 (91.7)	77 (86.5)	154 (89.0)
	Positive	6 (7.1)	11 (12.4)	17 (9.8)
Week 8	Negative	73 (86.9)	77 (86.5)	150 (86.7)
	Positive	9 (10.7)	10 (11.2)	19 (11.0)
Week 12	Negative	74 (88.1)	78 (87.6)	152 (87.9)
	Positive	9 (10.7)	10 (11.2)	19 (11.0)
Week 16	Negative	73 (86.9)	78 (87.6)	151 (87.3)
	Positive	7 (8.3)	8 (9.0)	15 (8.7)
Week 20	Negative	71 (84.5)	78 (87.6)	149 (86.1)
	Positive	9 (10.7)	7 (7.9)	16 (9.2)
Week 24/EOT	Negative	74 (88.1)	79 (88.8)	153 (88.4)
	Positive	7 (8.3)	7 (7.9)	14 (8.1)
Random tox 1	Negative	75 (89.3)	78 (87.6)	153 (88.4)
	Positive	8 (9.5)	8 (9.0)	16 (9.2)
Random tox 2	Negative	71 (84.5)	75 (84.3)	146 (84.4)
	Positive	10 (11.9)	9 (10.1)	19 (11.0)
Random tox 3	Negative	71 (84.5)	77 (86.5)	148 (85.5)
	Positive	8 (9.5)	9 (10.1)	17 (9.8)
Random tox 4	Negative	69 (82.1)	76 (85.4)	145 (83.8)
	Positive	11 (13.1)	9 (10.1)	20 (11.6)

Criteria Procedural Competency Insertion Procedure

PROBUPHINE® REMS PROGRAM TRAINER GUIDELINES: INSERTION PROCEDURE Trainees must demonstrate competency in performing the following techniques.		
	1	Identify insertion site (8-10 cm) above medial epicondyle of the humerus
	2	Clean the insertion site with alcohol prep.
	3	Mark insertion site with a marker (2.5 – 3.0 mm) and tracks for each implant with marker.
	4	Put on sterile gloves.
	5	Use aseptic technique to place sterile equipment and implants in sterile field.
	6	Clean incision sites with ChloraPrep for approx. 10 seconds each; swab three times.
	7	Apply sterile drape.
	8	Anesthetize insertion area.
	9	Check that the Obturator and cannula are functioning properly.
	10	After determining anesthesia is adequate and effective, lift skin with forcep, make a 2.5 – 3.0 mm shallow opening with scalpel.
	11	Insert cannula into the opening (not to exceed 20 degree angle) with bevel-up stop marking facing upwards until the proximal line is no longer visible under the opening.
	12	Insert one implant into cannula and re-insert the obturator and advance obturator until the marking reaches the bevel-up stop marking on cannula.
	13	Hold obturator fixed in place, retract cannula along obturator, and lock obturator.
	14	Stabilize the implant with finger while retracting the applicator to distal marking.
	15	Redirect applicator to the next channel marking and repeat steps 11-13.
	16	Verify presence of each implant by palpation.
	17	Clean incision site and apply liquid adhesive and steri-strips.
	18	Place small adhesive bandage over the insertion site.
	19	Apply pressure bandage with sterile gauze.
	20	Complete patient Identification Card and Chart Label.
	21	Discuss and provide patient a copy of wound care sheet and medication guide.

SL BPN Dose Distribution From Claims Data and Proprietary Patient Chart Comparison





Source: Symphony Health Solutions, Braeburn Patient Chart Review

RM-141

PROBUPHINE® (buprenorphine HCl) Implant CIII
Insertion/Removal Log Form

Treating Physician's Name:					
Treating Physician NPI or other Clinician ID:					
Patients ID:					
PROBUPHINE Kit #:					
Activity	**Clinician who insert or remove**		**Signature**	**Date**	**Notes**
	Name	**NPI or other clinician ID**			
PROBUPHINE Insertion					
PROBUPHINE Removal					
PROBUPHINE Disposal					
Please detail below actions taken to contact the patient including dates.					
No Removal Attempt to contact #1					
No Removal Attempt to contact #2					
No Removal Attempt to contact #3					
Care Transferred	**Name**	**NPI**	**Signature**	**Date**	**Notes**